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SYNTHESIS OF 2-(TETRAZOLO[1,5-A]QUINOLIN-4-YLMETHYLTHIO)BENZO[D]THIAZOLE AND ITS DERIVATIVES AS ANTIMICROBIAL AGENT

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ABSTRACT:
Synthesis of (2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole) was carried out in simple steps at very mild reaction conditions using 2-chloroquinoline-3-carbaldehyde and mercaptobenzothiazole as starting materials. The entire products formed were analyzed by 1H NMR, IR, and Mass for confirmation. The product was tested for microbial activity. The derivative of (2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole) shows antibacterial and antifungal activity which is comparable to the existing drugs like ampicillin, chloramphenicol, ciprofloxacin, greseofulvin.

KEYWORDS:
2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole, 2-chloroquinoline-3-carbaldehyde, Antibacterial, Antifungal, tetrazole, Mercaptobenzothiazole(MBT).

INTRODUCTION:

Heterocyclic compounds are essential components of many therapeutic core structures and play a significant role in biological and pharmacological processes[i]. Four out of the top five medications sold in the US are thought to contain heterocyclic compounds in their entity. Quinoline is an example of a bicyclic heterocyclic compound. The various known biological and pharmacological activities of functionalized quinoline moieties make them highly significant pharmacophoric motifs with undeniable therapeutic potential, which include antifungal,[ii] antibacterial,[iii] antimalarial,[iv-vi] anti-inflammatory,[vii] anticancer,[viii-x] antimicrobial,[xi-xiv] antihypertensive,[xv] DNA binding capacity,[xvi] anti tuberculosis,[xvii] antihistamine,[xviii] anti HIV,[xix] antiparasitic.[xx] The quinolines are modified with different ligand which makes its derivatives and shows more and better properties then quinoline itself. And so people are derivatising quinolines with different functional groups.

Tertazoles are one of the groups which have properties of antimicrobial,[xxi] central nervous system depressant,[xxii] anti-inflammatory,[xxiii] antifertility,[xxiv] anti-HIV,[xxv] Tetrazole groups have been compared to carboxylic groups as potential pharmacophores.[xxvi] Tetrazoles are used as angiotensin II receptor antagonists to treat high blood pressure,[xxvii] which is their main pharmaceutical use. The tetrazolo[1,5-a]quinoline-4-carbaldehyde serves as a key synthetic intermediate for the synthesis of novel medicinally valuable compounds,[xviii] and so plays an important role if we modified quinoline with it.

Worldwide, 2-mercaptobenzothiazole and its derivatives are produced for a wide range of uses. It is known to be linked to numerous biological functions. 2-MBT and its derivatives belong to a class of bioactive organic compounds that are essential for the industry.[xxix] mercaptobenzothiazole has antiviral,[xxx] antifungal.[xxxi] It is also used as a pesticide.[xxxii] In the rubber vulcanization,[xxxiii] and it has other application areas such as sensitizer [xxxiv] as well as in the leather industry. Considering the importance of quinoline, tetrazole, and 2-mercaptobenzothiazole combination of both may yield a product that will give much better activity for antifungal and antibacterial. So the strategies were planned for the synthesis of 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole from the starting material 2-chloroquinoline-3-carbaldehyde with four-step synthesis which includes reduction, chlorination followed by coupling reaction.

MATERIALS AND METHOD:

2-chloroquinoline-3-carbaldehyde prepared by the reported method, ethyl acetate, hexane, DCM, and methanol purchased from spectrochem, Avra chemicals, and S.D. fine chem, all the chemicals are used as received without any further purification. All physical constants were determined in open capillaries at atmospheric pressure. 1H NMR spectra were recorded on Bruker Avance using DMSO solvent at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR. Mass spectra analysis showing a molecular ion peak.

EXPERIMENTAL:

Synthesis of tetrazolo[1,5-a]quinoline-4-carbaldehyde (2a)

In 50 ml round bottom flask (RBF) 2-chloroquinoline-3-carbaldehyde 2.1 g (10.9 mmol) was taken, to this NaN_3(1.0 g) was added in 5 to 6 ml water with constant stirring, after successful addition of NaN_3 then 4 ml of acetic acid and 20 ml of DMSO was added at room temp. Stirring was kept constant for 3 h at 40°C. The reaction mixture was allowed to cool at room temperature for 12 h which yields white precipitate. Formed precipitate were filtered through Whatman filter paper and solid was recrystallized using acetone. (dry wt. 1.9 g, yield 87.5%)

Synthesis of tetrazolo[1,5-a]quinolin-4-ylmethanol (3a)

Synthesized tetrazolo[1,5-a]quinoline-4-carbaldehyde was used for the next step of synthesis of tetrazolo[1,5-a]quinolin-4-ylmethanol. Recrystallized 1.9 g, (9.5 mmol) of tetrazolo[1,5-a]quinoline-4-carbaldehyde taken in RBF (50 ml) and dissolved in 15 ml methanol. Sodium borohydride (0.25 g) was added slowly into the mixture at room temperature. The reaction was monitored by TLC using ethyl acetate: hexane (1:4) as the mobile phase. After the complete conversion of the reactant, methanol was removed and added ice cold water. A formed white solid was filtered and washed with ice-cold water and dried at 50°C and used for the next step synthesis (3a). (dry wt. 1.85 g, yield 96%)

Synthesis of 4-(chloromethyl)tetrazolo[1,5-a]quinoline (4a)

tetrazolo[1,5-a]quinolin-4-ylmethanol 1.8 g (8.9 mmol) was dissolved in 10 ml DCM in (50 ml) RBF. And in addition funnel, 3 ml thionyl chloride in 10 ml DCM was added to this solution in a dropwise manner. The reaction mass was heated at 40°C to get a complete conversion. The reaction was monitored by TLC ethyl acetate:hexane (1:4). After complete conversion the solvent is evaporated to get the product (4a). (dry wt. 1.85 g, yield 94%)

Synthesis of 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole (5a)

The mercaptobenzothiazole (8.5 mmol) was taken in 50 ml RBF, 10 ml methanol was added and stirred well, then 4-(chloromethyl)tetrazolo[1,5-a]quinoline 1.8 g (8.35 mmol) was added along with 5 to 6 drops of DBU at room temperature, reaction progress was monitored by TLC using ethyl acetate and hexane mixture (1:4). After completion of the reaction product was recovered by solvent evaporation washed with cold water and dried at 50°C. All the products formed were analyzed by 1H NMR, IR, and Mass for confirmation and identification. (5a) (dry wt. 1.9 g, yield 92%).

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY:

P. aeruginosa (MTCC-1688), E. coli (MTCC-443), S. aureus (MTCC-96), and S. pyogenes (MTCC-442) were used for the study of antibacterial activity, and For antifungal activities, A. Niger (MTCC-282) C. albicans (MTCC-227), and A. clavatus (MTCC-282) were utilised (MTCC1323). To cultivate and dilute the drug suspension for the test microorganisms, nutrient media such as Mueller Hinton Broth was utilised. This media was autoclaved at 120 °C for 30 minutes to sanitise it. It was then poured to a consistent 5 mm depth and allowed to harden. Using a sterile cotton swab, the surface was streaked with the microbial suspension (105 CFU/mL). Dimethyl sulphoxide was used to dissolve the produced compounds, resulting in a concentration of 3.25–1000 g/mL. Sterile filter paper discs measuring 6.25 mm in diameter were placed on nutritional agar and cultured with microorganisms for 24 hours for bacteria and 72 hours for fungi at 37 °C after being pre-soaked in a known concentration of the test substance in dimethyl sulphoxide. A control disc impregnated with an equivalent amount of dimethyl sulphoxide without any sample was also used and it did not result in any inhibition. Ampicillin and Geseofulvin were employed as checkpoint inhibitors. By using the agar streak dilution method, the MIC, or minimum bacterial inhibitory concentration, of a produced chemical is determined (Hawkey and Lewis 1994).

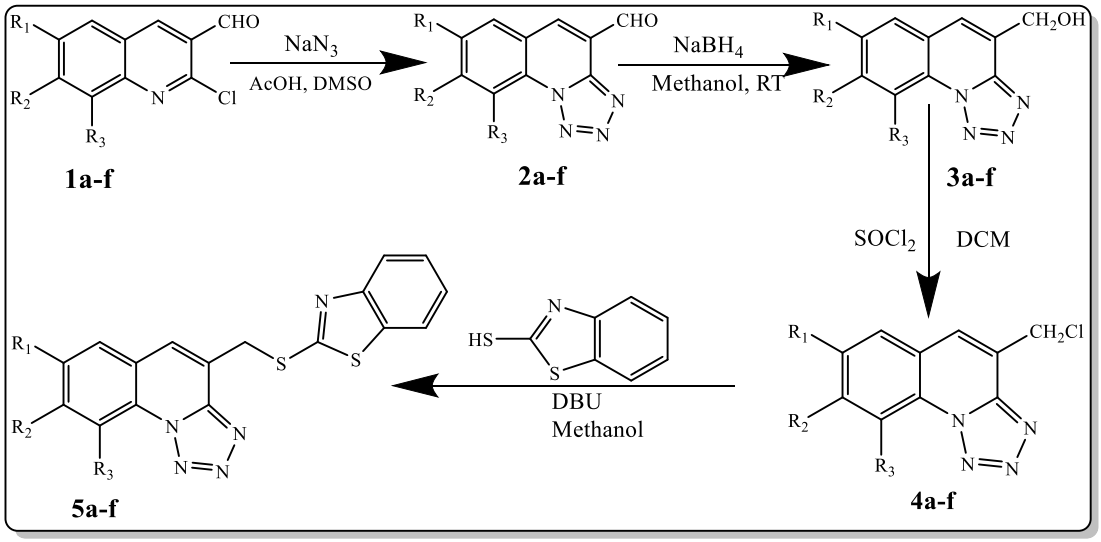
A predetermined amount of molten sterile agar and graded amounts of the produced compounds were added to a prepared stock solution in dimethyl sulphoxide for the evaluation of antibacterial activity and Sabouraud dextrose agar for the evaluation of antifungal activity. The medium containing the test substance was poured into the petri dish at a depth of 4-5 mm and allowed to harden to determine the septic state. The corresponding 105 CFU/mL microbe suspension was made, applied to plates, serially diluted with substances ranging from 3.1 to 1000 g/ml of dimethyl sulphoxide, and then incubated at 37°C for 24 hours for bacteria and 72 hours for fungi. Test run was three times; the lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC value.

RESULT AND DISCUSSION:

Here we report the simple and efficient way of synthesis of new 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole in good yield (Scheme-1). The detailed reaction is as follows Starting with the 2-chloroquinoline-3-carbaldehyde **1a-f** reacted with sodium azide in presence of acetic acid and DMSO at a 40°C temperature. The white solid product tetrazolo[1,5-a]quinoline-4-carbaldehyde formed in 80-86%. (Table 1, entries 1-6). Using the above-formed product the next step has proceeded. The reduction of tetrazolo[1,5-a]quinoline-4-carbaldehyde **2a-f** in presence of sodium borohydride and methanol. Reactions were carried out at room temperature to get the desired product tetrazolo[1,5-a]quinolin-4-ylmethanol **3a-f** in excellent yield (Table 1, entries 7-12). The formed product tetrazolo[1,5-a]quinolin-4-ylmethanol was reacted with thionyl chloride in the presence of dichloro methane. The reaction mixture was refluxed until the desired product 4-(chloromethyl)tetrazolo[1,5-a]quinoline **4a-f** was obtained (Table 1, entries 13-18).

For the final product formation the 4-(chloromethyl)tetrazolo[1,5-a]quinoline reacted with 2-mercaptobenzothiazole in methanol in presence of catalytic amount of DBU**.** The reaction

mixture was stirred at room temp. The progress of reaction was monitored by TLC (8:2-hexane; ethyl acetate). Product was recovered by solvent evaporation washed with cold water and dried. The synthesized compound **(5a-f)** obtained in an excellent yield (90-95%) (Table 1, entries 19-24). Analysis of all products by 1H NMR, IR and Mass shows the product are pure without any impurity with an excellent yields. The final product was used for the analysis of its antibacterial and antifungal properties. Their MIC values are reported in **Table-2,** the synthesized compound **5b**, **5c**, **5d**, and **5e** with methyl substitution at 9th, 8th, 7th and methoxy substitution at 8th position of quinoline respectively shows excellent antibacterial activity when compared with standard drug Ampicilline, Chloramphenicol and Ciprofloxacin. And shows moderate antifungal activity when compared with standard drug Greseofulvin.



Scheme-1: Synthesis of 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole derivatives

Table-1

Entry	Compound	R_1	R_2	R_3	Reaction Time(min)	Yield (%)	Melting Point(°C)
1	2a	H	H	H	180	87	241-242
2	2b	H	H	CH_3	180	86	222-223
3	2c	H	CH_3	H	180	83	225-226
4	2d	CH_3	H	H	180	85	231-232
5	2e	H	OCH_3	H	180	81	238-239
6	2f	OCH_3	H	H	180	82	225-226
7	3a	H	H	H	10	96	190-192
8	3b	H	H	CH_3	10	96	198-200
9	3c	H	CH_3	H	10	97	185-186
10	3d	CH_3	H	H	10	94	196-198
11	3e	H	OCH_3	H	10	98	230-232
12	3f	OCH_3	H	H	10	96	220-221
13	4a	H	H	H	30	94	202-204
14	4b	H	H	CH_3	30	94	178-180
15	4c	H	CH_3	H	30	93	182-184
16	4d	CH_3	H	H	30	95	188-190

17	4e	H	OCH_3	H	30	96	165-167
18	4f	OCH_3	H	H	30	97	185-187
19	5a	H	H	H	60	92	125-126
20	5b	H	H	CH_3	60	94	128-130
21	5c	H	CH_3	H	60	90	131-133
22	5d	CH_3	H	H	60	96	120-122
23	5e	H	OCH_3	H	60	95	165-167
24	5f	OCH_3	H	H	60	93	160-162

TABLE-2: ANTIBACTERIAL ACTIVITY STUDY OF SYNTHESIZED COMPOUNDS

Sr.NO..	Compound	MINIMAL BACTERICIDAL CONCENTRATION			
		E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
		MTCC-443	MTCC-1688	MTCC-96	MTCC-442
		MICROGRA/ML			
1	5a	500	250	500	**100**
2	**5b**	**100**	250	**25**	**50**
3	**5c**	500	200	**100**	**50**
4	**5d**	**62.5**	125	**150**	250
5	**5e**	250	**100**	**200**	500
6	5f	**100**	500	500	500

TABLE-3: ANTIFUNGAL ACTIVITY STUDY OF SYNTHESIZED COMPOUNDS

Sr.NO..	Compound	MINIMAL FUNGICIDAL CONCENTRATION		
		C.ALBICANS	A.NIGER	A.CLAVATUS
		MTCC-227	MTCC-282	MTCC-1323
		MICROGRAL/ML		
1	5a	1000	500	500
2	**5b**	**500**	1000	1000
3	5c	1000	>1000	>1000
4	**5d**	**500**	500	1000
5	5e	1000	>1000	>1000
6	**5f**	**500**	>1000	>1000

THE STANDARD DRUGS

DRUG	MINIMAL BACTERICIDAL CONCENTRATION			
	E.COLI	P.AERUGINOSA	S.AUREUS	S.PYOGENUS
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
	MICROGRAL/ML			
ERYTHROMYCINE	2	5	0.25	0.5
AMPICILLIN	100	100	250	100
CHLORAMPHENICOL	50	50	50	50
CIPROFLOXACIN	25	25	50	50
NORFLOXACIN	10	10	10	10

	MINIMAL FUNGICIDAL CONCENTRATION

DRUG	C.ALBICANS	A.NIGER	A.CLAVATUS
	MTCC-227	MTCC-282	MTCC-1323
	MICROGRAL/ML		
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

SPECTROSCOPIC DATA:

(5a) 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 3056.66 (=C-H), 1608.72 (C=C).

^{1}H NMR (DMSO, 400 MHz, δ ppm): 5.08 (s, 2H), 7.30-7.34 (m, 1H), 7.42-7.46 (m, 1H), 7.71-7.75 (m, 1H), 7.84-7.91 (m, 3H), 8.10-8.17 (m, 1H), 8.35-8.38 (d, 1H), 8.56-8.58 (d, 1H).

ESMS (m/z): 351.03.

(5b) 2-((9-methyltetrazolo[1,5-a]quinolin-4-yl)methylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 3034.93 (=C-H), 1621.66 (C=C), 2959.31 (C-H).

^{1}H NMR (DMSO, 400 MHz, δ ppm): 3.16 (s, 3H) 5.09 (s, 2H), 7.26-7.31 (m, 1H), 7.40-7.44 (m, 1H), 7.50-7.54 (m, 1H), 7.61-7.63 (m, 1H), 7.72-7.74 (m, 2H), 7.89-7.91 (d, 1H), 8.15 (s, 1H).

ESMS (m/z): 365.06.

(5c) 2-((8-methyltetrazolo[1,5-a]quinolin-4-yl)methylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 3045.53 (=C-H), 1608.52 (C=C)

^{1}H NMR (DMSO, 400 MHz, δ ppm): 3.21 (s, 3H) 5.07 (s, 2H), 7.21-7.30 (m, 1H), 7.45-7.51 (m, 1H), 7.55-7.61 (m, 1H), 7.66-7.69 (m, 1H), 7.75-7.79 (m, 2H), 7.88-7.92 (d, 1H), 8.21 (s, 1H).

ESMS (m/z): 365.09.

(5d) 2-((7-methyltetrazolo[1,5-a]quinolin-4-yl)methylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 3050.57 (=C-H), 1615.73 (C=C), 2975.88 (C-H).

^{1}H NMR (DMSO, 400 MHz, δ ppm): 2.53 (s, 3H), 5.07 (s, 2H), 7.26-7.31 (m, 1H), 7.41-7.45 (m, 1H), 7.60-7.63 (dd, 1H), 7.66 (s, 1H), 7.71-7.73 (dd, 1H), 7.90-7.92 (d, 1H), 8.09 (s, 1H), 8.48-8.50 (d, 1H).

ESMS(m/z): 365.06.

(5e) 2-((8-methoxytetrazolo[1,5-a]quinolin-4-yl)methylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 1617.77 (C=C), 1092.36 (C-O), 2899.67 (C-H).

^{1}H NMR (DMSO, 400 MHz, δ ppm): 4.02 (s, 3H) 5.07 (s, 2H), 7.21-7.23 (m, 1H), 7.26-7.31 (m, 1H), 7.40-7.44 (m, 1H), 7.71-7.73 (dd, 1H), 7.76-7.79 (dd, 1H), 7.89-7.91 (dd, 1H), 8.0 (dd, 1H), 8.11(s, 1H).

ESMS(m/z): 380.

(5f) 2-((7-methoxytetrazolo[1,5-a]quinolin-4-yl)methylthio)benzo[d]thiazole

IR (KBr, cm^{-1}): 1628.66 (C=C), 1038 (C-O), 2892.31 (C-H).

^{1}H NMR (DMSO, 400 MHz, δ ppm): 3.92 (s, 3H) 5.08 (s, 2H), 7.29-7.33 (m, 1H), 7.41-7.46 (m, 2H), 7.53-7.54 (d, 1H), 7.84-7.90 (m, 2H), 8.25 (s, 1H), 8.44-8.47 (d, 1H),

ESMS(m/z): 380.

CONCLUSION:

This work showed the synthesis of some 2-(tetrazolo[1,5-a]quinolin-4-ylmethylthio) benzo[d]thiazole derivative from 2-chloroquinoline-3-carbaldehyde and Mercaptobenzothiazole and confirmed the synthesized compounds by doing characterization 1H NMR, IR, MASS and carried out the antimicrobial activity of synthesized compounds. The antibacterial activity of some methyl substituted products is found to be excellent when

compared with standard drugs. Antifungal activity of compounds was found moderate with C. Albicans, A. Niger, and A. Clavatus when compared with standard Greseofulvin.

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