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Synthesis of new 4-((1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a] quinolines derivatives as antibacterial and antifungal agent

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Abstract: A new series of 4-(1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines have been synthesized by the reaction of 2-chloroquinolin-3-carbaldehydes and 1H-benzo[d]imidazole-2-thiol in quantitative yield. Structure of the newly prepared compounds have been determined by spectroscopic methods such as ^{1}HNMR, IR and Mass. Antifungal and antibacterial activities of these newly synthesized compounds have been studied. Antibacterial activity of newly synthesized compounds have been studied with S. aureus, E. coli, P. aeruginosa and S. pyogenes and was found good to moderate activities when compared with Ampicillin as standard. Antifungal activity of compounds was found good to moderate with C. Albicans, A. Niger and A. Clavatus when compared with standard Greseofulvin.

Keywords: 2-Chloroquinoline-3-carbaldehyde, antibacterial, antifungal, 4-((1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines, 1H-benzo[d]imidazole-2-thiol.

Introduction

Over the past decade, we have been primarily engaged in the synthesis of quinoline containing ring system, represents a very important and major class of heterocyclic compounds on the premise that quinoline sources is noticed in a large range of naturally occurring compounds and is used as a key intermediate for many pharmacologically important compounds.[1-2] The derivatives of quinoline broadly explored physiological and biological activities such as antimalarial,[3-6] anti-inflammatory,[7-10] antitumor,[11-12] DNA binding capacity,[13-14] antibacterial,[15-16] antimicrobial,[7-19] anticancer[20-21] anti-tuberculosis[22] antihistamine,[23] antifungal,[24] anti-HIV,[25] antihypertensive[26] and antiparasitic[27] properties. Also quinoline is used in the study of bioorganic and bioorganometallic processes [28]

As like the biological importance, the quinoline nucleus particularly, 2-chloroquinoline-3-carbaldehyde has been used as a key intermediate for the synthesis of building block of variety of medicinally valuable compounds. Meth-Cohn et al.[1] first described the synthetic utility of 2-choroquinoline-3-carbaldehyde. The 2-chloro group of the title compounds has been replaced by H, I, OH, SR, Li, COOH, CHO, Ph, piperidine and N_3 groups. The aldehyde group has also been converted into oxime, hydrazone, acrylic acid derivatives. From these and related derivatives a variety of fused quinolines have been made including –thieno, - pyridazino, -tropono, -pyrano and fluro-quinolines.

The benzimidazole is another important class of heterocyclic compounds, the derivatives of benzimidazole by synthesising hybrid molecules seeking the characteristics of these scaffolds in an attempt to discover potent agents such as antimicrobial,[29] antiviral,[30-31] anti-tumor,[32] anti-mutagens,[33] cardio-vascular,[34] anticalmodulin,[35] antiparkinsons,[36] anticancer,[37-38] antiinflammatory,[39] antiulcer[40] and many other activities are well documented.[41]

One of the component of vitamin B12 has been found as benzimidazole ring system and has received attention.[42] On the other hand, in the synthesis of wellknown proton pump inhibitors like pantoprazole,[43] omeprazole,[44] rabeprazole,[45]and lansoprazole[46] mercaptobenzimidazole is used in GERD as anti helicobacter agent.[47] Therefore benzimidazole acts as very important core structure for the drug design.[48]

The tetrazole group has considered analogous to car-boxylic group[49] as a pharmacophore. Several substituted tetrazoles show pronounced activities such as anti-fertility,[50] CNS depressant,[51] antimicrobial,[52] anti-inflammatory,[53] and antiaids.[54] The most prominent pharmaceutical application of tetrazoles is as angiotensin II receptor antagonists for the treatment of high-blood pressure.[55] The fusion of quinoline to the tetrazole ring is known to increase the biological activity.[56] In particular, tetrazolo[1,5-a]quinoline-4-carbaldehyde serves as a key synthetic intermediate for the synthesis of novel medicinally valuable compounds.[57-58]

Literature search reveals that very little attention has been made to get the combo benefit of these three paharmacophores. [59]

Thus, the important character displayed by quinolines, benzimidazole and tetrazole for various therapeutic and biological activities prompted us to synthesize some new derivatives of combining these three pharmacophores quinolone, benzimidazole and tetrazole in order to achieve compounds having better drug potential.

Our interest is to give some efforts in the direction to have synergic effects of the synthesized
combo pharmacophore from quinolines, benzimidazole and tetrazole for antibacterial and antifungal activities. Herein, we report a new protocol for the synthesis of 4-((1H-benzo[d]imidazol-2ylthio)methyl)tetrazolo[1,5-a] quinolines derivatives using 2–chloroquinoline–3-carbaldehyde and 1H

– benzo[d]imidazole-2-thiol.

Results and Discussion

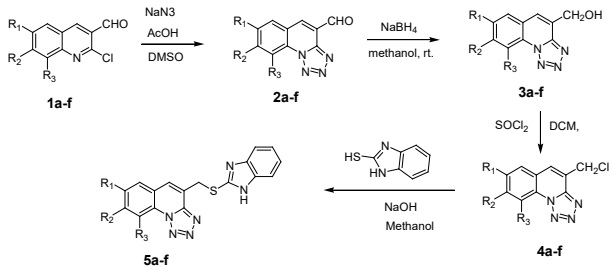
The present work involves the synthesis of Novel 4-((1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines derivatives by the chemical reaction of 2-chloroquinoline-3-carbaldehyde and 1H-benzo[d]imidazole-2-thiol (Scheme-1). The process includes the derivatives of tetrazolo[1,5a]quinoline-4-carbaldehyde 2a-f were prepared from substituted 2-chloroquinoline-3carbaldehyde 1a-f on treatment with sodium azide in the presence of acetic acid. The reactions were carried out using DMSO as a solvent at 40 °C. The products formed in 81–85% yields (Table 1, entries 1-6).

The synthesized tetrazolo[1,5-a] quinoline-4-carbaldehydes 2a-f on reduction with sodium borohydride at room temperature stirring in methanol formed the derivatives of (tetrazolo[1,5a] quinolin-4-yl)methanol 3a-f in excellent 94–97% yields within only 10 min (Table 1, entries 7–12).

These obtained derivatives of (tetrazolo[1,5-a]quinolin-4-yl)methanol 3a-f reacted with thionyl chloride in dichloromethane to form 4-(chloromethyl) tetrazolo[1,5-a]quinolines derivatives 4a-f in 95–98% yield and are entered in Table-1, entries 13-18. Above obtained derivatives of 4(chloromethyl) tetrazolo[1,5-a]quinolines 4a-f were reacted with 1H-benzo[d]imidazole-2-thiol in methanol in the presence of base like sodium hydroxide. Progresses of the reactions were monitored on TLC using mobile phase (8:2) hexane: ethyl acetate. The reaction proceeded smoothly under basic condition and completed in 1 hr to afford the corresponding titled compounds having entries 19–24 in Table -1 in high yields (85–95%). The chemical structures of the new compounds were confirmed by IR, ^{1}H NMR, mass spectroscopic data.

The newly prepared compound 5a-f have been studied for antibacterial activities using S. pyrogens, E. coli, S. aureus and P. aeruginosa with standard drug Ampicillin. The broth dilution technique was used for MIC values.Table-2 shows the MIC values of synthesized compounds. When compared with the standard drug Ampicillin (Table-4), the compounds shows good to moderate antibacterial activity with Gram +ve bacterial strains and Gram -ve strain.

The newly prepared compounds 5a-f were studied for antifungal activity using C. albicans, A.Clavatus and A. Niger with standard drug GreseofulvinTable-4 by broth dilution method and shown in Table-3. The compound shows good to moderate activities with C. albicans, A.Clavatus and A. Niger compared with Griseofulvin standard drug.



Scheme-1: Synthesis of 4-((1H-benzo[d]imidazol-2-ylthio) methyl)tetrazolo[1,5-a]quinolines derivatives

Materials and methods

In laboratory 2-chloroquinoline-carbaldehyde was prepared using reported method. Required solvents and reagents are purchased from spectrochem, Avra chemicals and S.D. fine chem. otherwise stated. Physical constants (melting point) were carried out in open capillaries at atmospheric pressure. Proton NMR was recorded on AVANCE in $CDCl_3$+DMSO and $CDC1_3$ at 300 MHz, 400 MHz using standard as TMS. Perkin- Elmer and Shimadzu FTIR were used for recording of IR spectra. Thermo exactiveorbitrap methods (FTMS) used for mass spectra analysis, showing a molecular ion peak. Institute of Microbial Technology, Chandigarh, India provided strains.

Experimental Procedure

Tetrazolo[1,5-a)quinoline-4-carbaldehyde (2a):

A mixture of 2-chloroquinoline-3-carbalde-hyde (10 mmol), sodium azide (1.0 g) in water (5 mL), acetic acid (2 mL), and dimethyl sulphoxide (100 mL) was stirred at 40 °C for 3 hr. The reaction mixture was allowed to remain at room temperature overnight. A white crystalline solid formed was filtered off, washed with water, dried, and recrystallized from acetone.

(Tetrazolo [1,5-a]quinolin-4-yl) methanol (3a):

To the stirred solution of tetrazolo[1,5-a] quinoline-4-carbaldehydes (10 mmol) in 15 mL methanol was slowly added sodium borohydride (0.25 g) at room temperature. The progress of reaction was monitored on TLC (8:2 Hexane:ethyl acetate). After the completion of the reaction (10 min), the reaction mixture was concentrated under reduced pressure to obtain residue. To this residue, ice cold water was added and the solid obtained was filtered off to get product.

4-(Chloromethyl)tetrazolo[1,5-a] quinoline (4a):

To the stirred solution of (tetrazolo[1,5-a] quinolin-4-yl)methanol (10 mmol) in DCM (10 mL) was added dropwise à solution of $SOC1_2$ (2 mL) in 5 mL DCM. After the complete addition, and stirred it for 1 h at room temperature. The reaction progress was monitored by the TLC (8:2 Hexane:ethyl acetate), after complete conversion, distilled out the solvent in a rota-evaporator under reduced pressure to get the product. 96%, which was enough pure and used directly for the next step

4-((1H-benzo[d]imidazol-2-ylthio) methyl)tetrazolo[1,5-a]quinolines (5a)

To the solution of 1H-benzo(d)imidazole-2thiol 1.48 gm, 10 mmol in methanol 20 mL added sodium hydroxide 0.6 gm, 15 mmol. To this pre-stirred (10 min) solution 4 (Chloromethyl) tetrazolo[1,5-a]quinoline, 9 mmol added at room temperature and stirred for 1 hr. The reaction progress checked on thin layer chromatography using Hexane and ethyl acetate as solvent system (8:2). After complete conversion of reaction mass, the solvent removed under vacuum on rota evaporator. To the obtained residue cold water 100 mL added, filtered solid and washed with water 50 mL to get product, which is dried on rotary evaporator. Dried compound purified on column chromatography by using hexane

and ethyl acetate solvent to get the titled compound, 87%.

IR (cm^{-1}): 3505(-NH); 2968 (-C-H); 1613 (-C=C);

^{1}H NMR (DMSO, δppm): 5.00 (s, 2H), 7.08 – 8.56 (m, 9H),
ESMS: 333.02 (m+1) m/z and 331.14 (m-1) m/z

Similar procedure was applied for the preparation of compounds (5b-f) using an appropriate quantity of reagents

Compound (5b)

4-((1H-benzo[d]imidazol-2-ylthio) methyl)-9-methyltetrazolo[1,5-a] quinoline

IR (cm^{-1}): 3409 (-NH), 2979 (-C-H), 1622 (-C=C),

^{1}H NMR (DMSO, δppm): 2.44 (s, 3H), 4.97 (s, 2H), 7.09–8.36 (m, 8H),
ESMS: 347.07 (m+1) m/z and 345.18 (m-1) m/z

Compound (5c)

4-((1H-benzo[d]imidazol-2-ylthio) methyl)-8-methyltetrazolo[1,5-a] quinolines

IR (cm^{-1}): 3342 (-NH), 2897 (-C-H), 1613 (-C=C),

^{1}H NMR (DMSO,δppm):2.53 (s, 3H), 4.97 (s, 2H), 7.09–8.32 (m, 8H),
FTMS: 347.07 (m+1) m/z and 345.18 (m-1) m/z

Compound (5d)

4-((1H-benzo[d]imidazol-2-ylthio) methyl)-7-methyltetrazolo[1,5-a] quinolines

IR (cm^{-1}): 3379 (-NH), 2930 (-C-H), 1608 (-C=C),

^{1}H NMR (DMSO,δppm): 2.44 (s, 3H), 4.97 (s, 2H), 7.09–8.36 (m, 8H),
ESMS: 347.07 (m+1) m/z and 345.18 (m-1) m/z

Compound (5e)

4-((1H-benzo[d]imidazol-2-ylthio) methyl)-8-methoxytetrazolo[1,5-a] quinoline

IR (cm^{-1}): 3391 (-NH), 2975 (-C-H), 1615 (-C=C),
^{1}H NMR (DMSO,δppm): 4.01 (s, 3H), 4.97 (s, 2H), 7.08–8.17 (m, 8H),
ESMS: 363.06 (m+1) m/z and 361.17 (m-1) m/z

Compound (5f)

4-((1H-benzo[d]imidazol-2-ylthio) methyl)-7-methoxytetrazolo[1,5-a] quinolines

IR (cm^{-1}): 3576 (-NH), 2973 (-C-H), 1621 (-C=C),

^{1}H NMR (DMSO, δppm): 3.89 (s, 3H), 4.99 (s, 2H), 7.09–8.43 (m, 8H),
ESMS: 363.06 (m+1) m/z and 361.17 (m-1) m/z

Antibacterial and Antifungal activity:

The study of antibacterial activity was carried out with p. aeruginosa (MTCC-1688), E. coli (MTCC-443), S. aureus (MTCC-96) and S. pyogenes (MTCC-

442), and also the antifungal study was carried out with A. Niger (MTCC-282) C. albicans (MTCC-227), and A. Clavatus (MTCC1323). Nutrient medium as Mueller Hinton Broth was used to grow and dilute drug suspension for test bacteria. This media sterilized in autoclaved at 120 °C for half hour, poured with uniform depth 5 mm and allowed to solidify.

The microbial suspension 105 CFU/mL was streaked over the surface using sterile cotton swab. The prepared compounds dissolved in dimethylsulphoxide to give the concentration 3.25–1000 µg/mL. Sterile filter paper discs of diameter 6.25 mm was previously soaked in known concentration of respective test compound in dimethylsulphoxide and placed on nutrient agar that was incubated microorganisms and incubated for 24 hr for bacteria and 72 hr for fungi at 37 °C. A control disc impregnated with an equivalent amount of dimethylsulphoxide without any sample was also used and did not produce any inhibition. Greseofulvin and Ampicillin were used for control drugs. MIC minimum bacterial inhibitory concentration of prepared compound determined by agar streak dilution method (Hawkey and Lewis 1994).

Prepared stock solution in dimethylsulphoxide and graded quantities of the prepared compounds were incorporated in aspecified quantity of molten sterile agar for evaluation of antibacterial activity and Sabouraud dextrose agar for antifungal activity. In the petri dish the medium containing test compound was poured at depth of 4-5 mm and allowed to solidify for septic condition. The respective microorganism suspension of 105 CFU/mL prepared and applied on plates serially diluted compounds with concentrations in the range of 3.12–1000µg/ml in dimethylsolphoxide and were incubated for 24 hr for bacteria and 72 hr for fungi at 37°C. Test run was triplicates; the lowest concentration of the substance that prevents the development of visible growth is considered to be the MIC value.

Table-1: Data of newly synthesized compounds

Entry	Compound	R_1	R_2	R_3	Reaction Time(min)	Yield(%)	Melting Point (^{0}C)
1	2a	H	H	H	180	81	240-241
2	2b	H	H	CH_3	180	85	223-224
3	2c	H	CH_3	H	180	82	225-226
4	2d	CH_3	H	H	180	83	230-231
5	2e	H	OCH_3	H	180	82	238-239
6	2f	OCH_3	H	H	180	81	226-227
7	3a	H	H	H	10	96	189-190
8	3b	H	H	CH_3	10	94	199-200
9	3c	H	CH_3	H	10	96	185-186
10	3d	CH_3	H	H	10	96	195-196
11	3e	H	OCH_3	H	10	97	231-232
12	3f	OCH_3	H	H	10	96	219-220
13	4a	H	H	H	30	96	202-204
14	4b	H	H	CH_3	30	96	177-179
15	4c	H	CH_3	H	30	97	181-183
16	4d	CH_3	H	H	30	97	188-190

17	4e	H	OCH_3	H	30	97	166-168
18	4f	OCH_3	H	H	30	95	185-187
19	5a	H	H	H	60	87	220-222
20	5b	H	H	CH_3	60	89	200-202
21	5c	H	CH_3	H	60	91	208-210
22	5d	CH_3	H	H	60	90	231-233
23	5e	H	OCH_3	H	60	91	196--198
24	5f	OCH_3	H	H	60	89	210-212

Table-2: Antibacterial Activity study of newly synthesized compounds

Sr. No.	Compounds	Minimal Bactericidal Concentration			
		E. Coli	P. Aeruginosa	S. Aureus	S. pyogenus
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442
		µg/mL			
1	5a	100	125	100	50
2	5b	125	250	100	250
3	5c	125	250	500	250
4	5d	100	500	500	250
5	5e	62.5	250	100	50
6	5f	500	250	100	250

Table-3: Antifungal activity study of newly synthesized compounds

Sr. No.	**Compounds**	**Minimal Fungicidal Concentration**		
		C. Albicans	**A. Niger**	**A.Clavatus**
		MTCC 227	MTCC 282	MTCC 1323
		µg/mL		
1	5a	250	500	500
2	5b	500	1000	1000
3	5c	> 1000	> 1000	> 1000
4	5d	> 1000	> 1000	> 1000
5	5e	500	500	500
6	5f	> 1000	> 1000	> 1000

Table-4: Antibacterial and antifungal activities of standard drugs

Drug	**Minimal Bactericidal Concentration**			
	E. Coli	**P. Aeruginosa**	**S. Aureus**	**S. pyogenus**
	MTCC 443	**MTCC 1688**	**MTCC 96**	**MTCC 442**
	µg/mL			
Erythromycin	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

Drugs	Minimal Fungicidal Concentration		
	C. Albicans	A. Niger	A.Clavatus
	MTCC 227	MTCC 282	MTCC 1323
	µg/mL		
Nystatin	100	100	100
Greseofulvin	500	100	100

Conclusion

A new serise of 4-(1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a] quinolines have been synthesized by the reaction of 2-chloroquinolin-3-carbaldehydes and 1H-benzo[d] imidazole-2-thiol in quantitative yield. Structure of the newly prepared compounds have been determined by spectroscopic methods such as ^{1}HNMR,

IR and Mass. Antibacterial activity of newly synthesized compounds have been studied with S. aureus, E. coli, P. aeruginosa and S. pyogenes and was found good to moderate activities when compared with Ampicillin as standard. Antifungal activity of compounds was found good to moderate with C. Albicans, A. Niger and A. Clavatus when compared with standard Greseofulvin.

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