WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 7, Issue 1, 760-767 Research Article ISSN 2278 – 4357

SYNTHESIS & ANTIBACTERIAL ACTIVITY OF 2(2'-THIONE-4'(3'H)-QUINAZOLINONYL) 6'-FLUORO-7'-CHLORO-2'-IMINO (1,3) BENZOTHIAZOL DERIVATIVES

Ekta Pandey[1] and Niladry Sekhar Ghosh[2*]

[1]Bundelkhand Institute of Engineering & Technology Jhansi UP-284128.

[2]School of Pharmaceutical Sciences Bahra University, Solan HP-173234.

Article Received on
26 October 2017,

Revised on 14 Nov. 2017,
Accepted on 06 Dec. 2017

DOI: 10.20959/wjpps20181-10719

***Corresponding Author**
Niladry Sekhar Ghosh
School of Pharmaceutical Sciences Bahra University, Solan HP-173234.

ABSTRACT

In present work, flurochloro amiline was treated with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluro-7-chloro (1,3)-benzothiazole, which was treated with hydrazine hydrate (99%) in the presence of concentrate HCl using ethylene glycol as solvent to get 2-hydrazino-6-fluro-7-chloro(1,3) benzothiazoles, which was condensed with antranilic acid presence of dry pyridine to get 2-amino N-(2'amino (1',3') benzothiazolyl 6'-fluoro-7'-chloro) 4-(3H)-quinazoline. The above condensed product was treated with carbon disulphide in the presence of alcoholic potassium hydroxide to get 2(2'-thione-4'(3'H)-quinazolinonyl) 6'-fluoro-7'-chloro-2'-imino (1,3) benzothiazole. To this above product different aromatic aniline, PABA, piperzino, diphenylamine, N-Methyl piperzino, O-toludine in presence of DMF were treated to get newly synthesized compound through replacing at 7th position chlorine. The lead compounds of scheme I were characterized by melting point, TLC, calculated elemental analysis, UV, IR and ^{1}HNMR spectral studies. Further they have screened for their antibacterial activity.

KEYWORDS: Fluorine, Benzothiazole, Quinazoline. Antibacterial.

INTRODUCTION[1-2]

It is well known that the introduction of fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electronegativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Therefore it was thought

worthwhile to synthesize better kinds of drugs by incorporating quinazoline and fluorine atom in benzothiazole moiety.

In search for new bioactive potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the quinazoline nucleus and study their biological and pharmacological activity, the review of literature reveal prompted us to synthesis substituted Fluoro-benzothiazolyl quinazoline compounds and those will be screened for antimicrobial, anti-inflammatory and anticonvulsant activity to get potent bioactive molecule.

The wide range of biodynamic properties shown by fluorobenzenes, 2-substituted benzothiazoles prompted us to synthesized 2[2'-thione-4'(3'H)-quinazolinonyl)-6-fluoro-7-substituted-2-amino (1,3)benzothiazole) in hope of getting potent biodynamic agents

MATERIAL AND METHODS

The scheme of general methodology for preparation of fluoro benzothiazole derivatives method was determine & identified by physical constants, solubility tests, TLC and structural conformations by UV, IR, NMR, MASS spectral studies are described in the experimental section and spectral studies.

First Step

General synthesis of 2-amino-6-fluoro-7-chloro-benzothiazole[3-9]

To glacial acetic acid (20ml) cooled below room temperature were added 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of fluoro chloro aniline. The mixture was placed in freezing mixture of ice and salt and mechanically stirred while 1.6ml of bromine in 6ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond room temperature. After all the bromine was added (105min), the solution was stirred for 2 hours below room temperature and at room temperature for 10 hours, it was then allowed to stand over night, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0c on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid heated again to 85^0c and filtered hot. The combined filtrate was cooled and neutralised with concentrated ammonia solution to p^H 6 A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow plates of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole. After drying in a oven at 80^0C, the dry material (1gm 51.02%) melted at 210-212^0c.

Second Step

Synthesis of 2-hydrazino-6-fluoro-7-chloro-(1,3)-benzothiazole[3,12]

Concentrated hydrochloric acid (HCl) 10 ml was added drop wise with stirring to hydrazinehydrate (0.2 mol) at 5-10°C followed by ethylene glycol (40 ml).

To the above solution, 2-amino-6-fluoro-7-chloro benzothiazole (0.01mol) was added in portions and resultant mixture was refluxed for 2 hrs and cooled. The solid separated was crystallized from ethanol (Yield 76%).

Third Step

Synthesis of 2-amino N-(2'-amino(1',3')benzothiazolyl-6'-fluoro-7'-chloro)-4-(3H)-quinazolinone

Antranilic acid 4 gm (0.029 mol) and 2-hydrazino-6-fluro-7-chloro(1,3) benzothiazole 5.6 gm (0.026 mol) were dissolved in dry pyridine (30 ml). The solution was refluxed for 8 hrs. The solution was cooled and poured in ice water. The separated mass was filtered, washed with water and dried. The product was recrystallized from ethanol.

Fourth Step

Synthesis of 2-(2'-Thione 4'-(3'H)-quinazolinonyl) 6-fluoro-7-chloro-2-imino(1,3) benzothiazole

To an ice cold solution of pot hydroxide (0.1 gm 0.02 mol) in dry ethanol (50 ml), step-III (third step) product (2.6 gm, 0.008 mol) and carbon disulphide (6 ml, 0.078 mol) was added with stirring. The solution was refluxed for 10 hrs. and cooled. The quantity of solvents was reduced by distillation. The separated solid was filtered, washed with dry ether and dried. The product was recrystallized from ethanol.

Fifth Step

Synthesis of 2-(2'-Thione 4'-(3'H)-quinazolinonyl) 6-fluoro-7-substituted-2-imino(1,3) benzothiazole

The 0.007 mol of 2-(2'-Thione 4'-(3'H)-quinazolinonyl) 6-fluoro-7-chloro-2-imino(1,3) benzothiazole was treated with equimolar quantity (0.0075 mol) of various substituted aromatic anilines, PABA, morpholine, piperazine dimethyl amine, diphenylamine and refluxed for 2 hrs. in presence of DMF (dimethyl formamide) then the mixture was cooled and poured into crused ice.

The solid separated was filter off, dried and recrystallised from benzene and super dry alcohol (1:1).

Antibacterial activity[13-16]

The selected compounds prepared in the course of present investigation was screened for antibacterial activity against the following bacteria.

1) *Staphylococus aureus (Gram +ve).*
2) *Escherichia coli (Gram -ve).*
3) *Bacillas subtilis (Gram +ve).*
4) *Pseudomonas (Gram -ve).*

The antibacterial activities are performed by cup plate method (diffusion technique).The standard drugs and synthesized compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted and made up the volume with distilled water to get 50 □ g/ml and 100□ g/m concentrations. The procaine penicillin used against *Staphylococcus aureus, Bacillas subtilis* and streptomycin used against *Escherichia coli, Pseudomonas* as standard drugs.

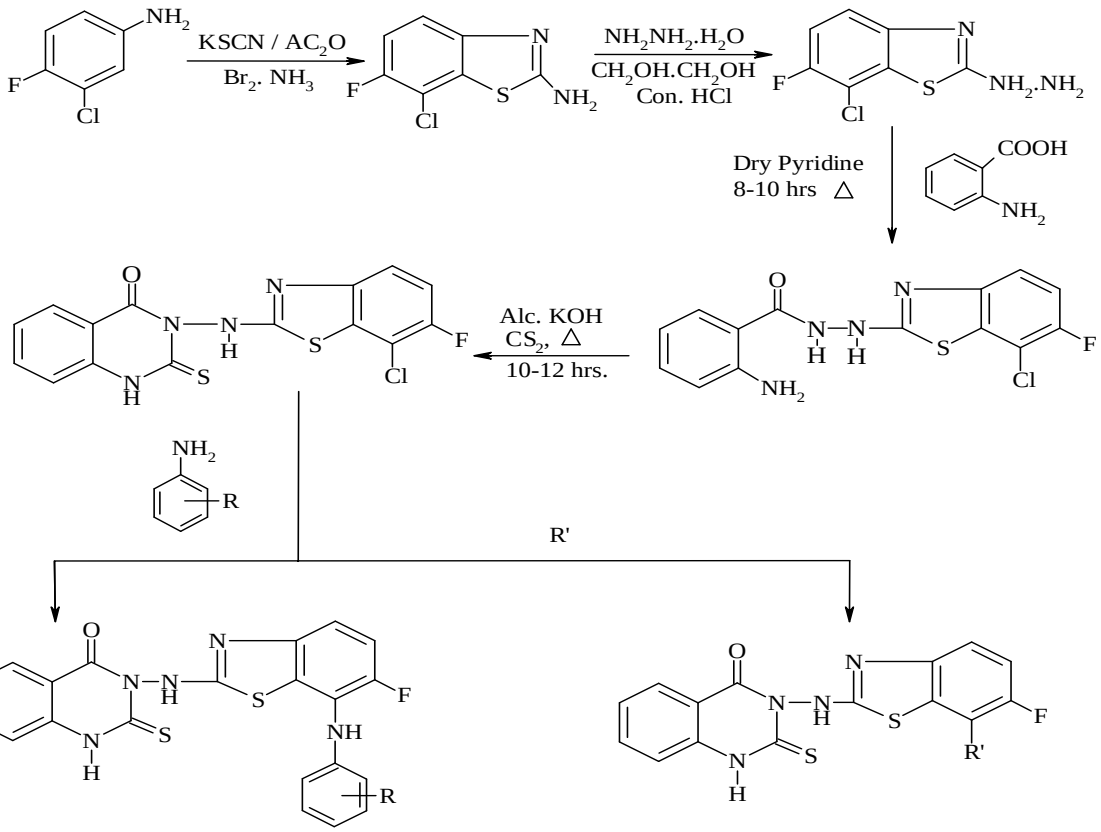
RESULTS AND DISCUSSION

Synthesized compounds were tested for the antibacterial activity against following bacteria.

a) i] *S.aureus*, ii] *B.substillis* (gram +ve*)* and
b) iii] *E.coil*, iv] *Pseudomonas* (gram –ve).

The test compounds VH_4, VH_6 showed moderate antibacterial activity against *S.aureus* (gram +ve) compare to standard drug procaine penicittin. Compounds VH_2, VH_6, VH_9, VH_{10} showed promising antibacterial activity against, *E. coli* (gam –ve) compared to standard drugs and steptomycin. Compounds VH_3, VH_4, showed promising antibacterial activity against, gam +ve (*B.subtillis*) at lower concentration (50 μg/ml). Compound VH_{11}, VH_{12} showed moderate activity against gm –ve (*Pseudomonas*) at both lower and higher concentration compare to standard drug steptomycin.

SCHEME



R = o, m, p- nitro aniline (H_1 - H_3)

= o, m, p- chloro aniline (H_4 – H_6)

= N- phenyl (H_9)

= o-ethyl, p-carboxyl (H_{10} – H_{11})

R' = morpholine, piperazine

= N-methyl piperazine

Analytical Data

Table 1.

Sl. No	Comp. Code	M.P/ B.P°C	% Yield	MOL. FORM	M.Wt.	C%	H%	N%
1	V H_1	170-171	86	$C_{21}H_{13}O_3S_2N_6F$	480	52.50	2.70	17.50
2	V H_2	196.198	80	$C_{21}H_{13}O_3S_2N_6F$	480	52.50	2.70	17.50
3	V H_3	145-146	78	$C_{21}H_{13}O_3S_2N_6F$	480	52.50	2.70	17.50
4	V H_4	132-133	82	$C_{21}H_{13}OS_2N_5ClF$	469.5	53.67	2.76	14.90
5	V H_5	194-196	85	$C_{21}H_{13}OS_2N_5ClF$	469.5	53.67	2.76	14.90
6	V H_6	194-196	78	$C_{21}H_{13}OS_2N_5ClF$	469.5	53.67	2.76	14.90
7	V H_7	216-218	74	$C_{19}H_{12}O_2S_2N_5F$	425	53.64	2.82	16.47
8	V H_8	165-166	78	$C_{19}H_{17}OS_2N_6F$	428	53.27	3.97	19.62
9	V H_9	154-155	78	$C_{27}H_{18}OS_2N_5F$	511	63.40	3.52	13.69
10	V H_{10}	134-136	82	$C_{22}H_{16}OS_2N_5F$	449	58.79	3.56	15.59
11	V H_{11}	172-174	83	$C_{22}H_{14}O_3S_2N_5F$	479	55.11	2.92	14.61
12	V H_{12}	195-197	87	$C_{20}H_{19}OS_2N_6F$	442	54.29	4.29	19.00

Table No. 2: Characteristics IR absorption bands of similar compounds (VH_1 to VH_{12}) are tabulated below.

Sl. No.	Compound code	Ar-NH_2 stret cm^{-1}	ArC=C cm^{-1}	C=N cm^{-1}	C-F cm^{-1}	N-H cm^{-1}	C=O cm^{-1}	C=S cm^{-1}	C-Cl cm^{-1}	NO_2 cm^{-1}	CH_3 cm^{-1}	Benzo thiazole cm^{-1}
1	V H_1	3467	1445	1601	1168	3308	1690	1566		706		1404
2	V H_2	3464	1460	1600	1188	3290	1676	1555		706		1401
3	V H_3	3464	1452	1606	1188	3290	1676	1555		710		1400
4	V H_4	3464	1452	1606	1168	3300	1670	1558	719	-		1400
5	V H_5	3464	1458	1610	1194	3290	1670	1568	719	-		1404
6	V H_6	3470	1458	1610	1194	3308	1670	1548	719	-		1404
7	V H_7	3446	1444	1610	1194	3315	1676	1548				1404
8	V H_8	3460	1445	1610	1206	3330	1675	1560				1404
9	V H_9	3474	1440	1606	1200	3330	1676	1548				1404
10	V H_{10}	3468	1440	1600	1186	3300	1686	1555	-	-	1306	1415
11	V H_{11}	3477	1452	1606	1200	3345	1676	1550				1404
12	V H_{12}	3477	1452	1610	1186	3320	1676	1560				1404

Table 3: NMR Spectral Data of Compounds VH_3, VH_6, VH_7, VH_9.

Sl. No.	Spectra No.	Compound Code	Hydrogen	δ (ppm)	Multiplity	Solvent
1	36	VH_3	-10H, -Ar-H -1H, -NH -1H, -NH	6.5-8.2 5.3 7.1	Multiplet Singlet Singlet	$CDCl_3$
2	37	VH_6	-10H, -Ar-H -1H, -NH -3H, -NH	7.0-7.6 5.2-5.6 7.0-7.2	Multiplet Singlet Singlet	$CDCl_3$
3	38	VH_7	-10H-Ar-H -8H-CH_2 -2H-NH -2H-NH	7.0-7.6 1.5 5.3 7.1	Multiplet Singlet Singlet Singlet	$CDCl_3$
4	39	VH_9	-16H-Ar-H -3H-NH -3H-NH	6.9-7.6 5.3 7.1	Multiplet Singlet Singlet	$CDCl_3$

Table No. 4: Antibacterial activity.

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)			
		Staphylococcus aureus		*Escherichia coli*	
		50µg	100µg	50µg	100µg
	Procaine penicillin	20	24	-	-
	Streptomycin	-	-	21	25
	V H_1	9	13	14	17
01	V H_2	10	12	17	17
02	V H_3	10	13	13	14
03	V H_4	13	15	16	18
04	V H_5	12	15	14	14
05	V H_6	13	15	18	17
06	V H_7	10	15	12	14
07	V H_8	11	13	11	12
08	V H_9	11	13	19	19
09	V H_{10}	12	14	20	21
10	V H_{11}	10	13	9	11
11	V H_{12}	10	13	14	16

Table No. 5: Antibacterial activity.

Sl. No	Name of the compounds	Mean zone of inhibition (in mm)			
		B. subtilis		*Pseudomonas*	
		50µg	100µg	50µg	100µg
	Procaine penicillin	20	24	-	-
	Streptomycin	-	-	20	25
01	V H_1	11	11	10	11
02	V H_2	11	11	11	12
03	V H_3	15	15	11	12
04	V H_4	15	15	13	15
05	V H_5	13	14	11	15
06	V H_6	11	13	14	14
07	V H_7	11	13	12	13
08	V H_8	14	14	11	11
09	V H_9	11	11	11	13
10	V H_{10}	12	12	10	13
11	V H_{11}	10	10	13	15
12	V H_{12}	11	10	15	15

CONCLUSION

The lead compounds of scheme I were characterized by melting point, TLC, calculated elemental analysis, UV, IR and ^{1}HNMR spectral studies. The compounds were tested for antibacterial activity.

VH_4, VH_6, VH_7, VH_8 showed promising antibacterial activity at low & high concentration compare to standard.

REFERENCES

1. FILLER RJ. Fluorine Chem, 1986; 33: 361-375.
2. Greco Micheal N, Hangman William E. Chem Abstr, 1992; 117: 131109 z.
3. Jayachandran E, Naragund LVG, Shivkumar B, Kamal Bhatia. Ori J Chem, 2003; 19(1): 139-42.
4. Gopkumar P, Jayachandran E, Nagappa AN, Shivkumar B, Nargund LVG, Gurupadiah BM. Ind J Heterocyclic Chem, 2001; 11: 39-42.
5. Pattan SR, Narendra Baba SN, Jayashri Angadi. Ind J Heterocyclic Chem, 2002; 11: 333-334.
6. Joshy CL, Purushothaman E. Ind J Heterocyclic Chem, 2002; 12: 69-70.
7. Sreenivasa Murthy V, Jayachandran E, Nargund LVG. Indian Drugs, 1999; 36(2): 137-139.
8. Gurupadaiah BM, Jayachandran E, Shivakumar B, Nagappa AN, Nargund LVG. Ind J Heterocyclic Chem, 1998; 7: 213.
9. Murthy VS, Nagappa AN, Nargund LVG. Ind J Heterocyclic Chem, 1998; 8: 23.
10. Chakole RD, Amenkar ND, Khedekar PB, Bhusarik P. Indian J Heterocyclic Chem 2005; 15: 27-30.
11. Chakole RD, Amenkar ND, Khedekar PB, Bhusarik P. Indian J Heterocyclic Chem, 2006; 1: 217-220.
12. Srinivasa GM, Jayachandra E, Shivakumar B, Sreenivasa Rao D. Oriental J Chem, 2004; 20(1); 103-110.
13. Robbert D, Smyth. Clinical analysis, Microbiology, Remington's Pharmaceutical sciences, 18th ed. Mack Publishing company, peninisilvenia, 1991; 524-27.
14. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Society of Clinical Microbiology and Infectious Diseases (ESCMID), 2000.
15. Jayachandra E, Naragund LVG, Shivakumar B, Kamal Bhatia. Oriental J Chem, 2003; 19(1): 139-142.
16. Srinivasa Kumar M, Ramasharma GVS. Indian J Heterocyclic Chem, 1998; 7: 281-284.