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SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-FLUORO BENZOTHIAZOLE SUBSTITUTED QUINAZOLINES

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ABSTRACT

In the present work, 2-amino benzothiazoles were synthesized from 3-chloro-4-fluoro aniline and further condensed with Anthranilic acid and acetic anhydride to yield the corresponding Benzothiazole substituted Quinazolinone derivative. The formed Quinazoline derivative was treated with formaldehyde and diethylamine to yield benzothiazole substited diethylamino Quinazoline derivative. The formed derivatives were further condensed with different primary and secondary amines. The synthesized compounds were confirmed by spectral analysis such as IR, ^{1}H-NMR, Mass and were screened Anti-microbial activity.

KEY WORDS: 2-Aminobenzothiazole, Quinazolone, Anthranilic acid, Anti-microbial activity.

1. INTRODUCTION

The chemistry and biological study of heterocyclic compounds has been an interesting field in medicinal chemistry for a long time. 2-amino benzothiazole, a heterocyclic compound containing N and S atoms serve as a unique and versatile scaffold for experimental drug design (Shiwani Jaiswal and Abhinav, 2012) and have varied biological activities like anti-inflammatory, anti-tumour (Shashank, 2009), anthelmintic (Bushan Kumar, 2006), anti-tubercular (Raga Basawaraj, 2010), anti-convulsant (Velmurugan, 2012) and antimicrobial (Priyanka Yadav, 2010). Quinazole is the key structure in numerous compounds. Quinazolines can be prepared from Anthranilic acid. They represent an important class of compounds not only for their theoretical interest but also for their biological activities such as anti-inflammatory (Pritesh Patel, 2012), hypoglycemic (Garg, 1971), anti-viral (Karale, 2007) and diuretics (Lara Bianchi, 2003). In present study, a novel series of diethyl amino-Quinazoline derivatives were synthesized from benzothiazoles and were screened for antimicrobial activity.

2. MATERIALS AND METHODS

Experimental: The synthesized compounds are first purified by re-cyrstallisation using appropriate solvents. The melting points were determined in an open capillary tube and are uncorrected. The IR spectra were recorded on ABB BOMEM FTIR Spectrometer using KBr disc of the sample. The NMR spectra were recorded as 400MHz NMR Spectrometer in DMSO using TMS as an internal standard. Chemical shift is given in δppm.

Synthesis of 2-amino-6-fluoro-7-chloro (1,3) benzothiazole: 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(Compound 1). The mixture was placed in a water bath and stirred with magnetic stirrer 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 rises 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 overnight, during which period an orange precipitate settle at the bottom, water (6ml) was added quickly and slurry was heated at 85^0C 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 ammonia solution to the pH range 6.0 A dark yellow precipitate was collected. Recrystalised from benzene, ethanol of (1:1) after treatment with animal charcoal gave yellow crystals of 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole.

Synthesis of benzothiazole substituted Quinazoline moiety: Anthranilic acid (0.01mol) and acetic anhydride were refluxed under anhydrous condition for 4hrs. Excess of acetic anhydride was distilled off under reduced pressure. To the mixture obtained, 2-amino-7-chloro-6-fluoro benzothiazole (0.01mol) in glacial acetic acid was added and refluxed for 4hrs and the obtained reaction mixture was poured into crushed ice and kept overnight. The solid separated out was filtered, thoroughly washed with cold distilled water, dried and re-crystallized from ethanol (95%).

Synthesis of substituted Quinazolones: A mixture of Compound 2(0.01mol), formaldehyde (40%, 1.5ml) and diethyl amine (0.01mol) were stirred for 4hrs in presence of methanol and left overnight at room temperature. The solid mass separated was collected by filtration, washed with ethanol, dried and re-crystallized.

Synthesis of 3-(7-chloro-6-fluoro-1,3-benzothiazol-2-yl)-1-((diethyl-amino) methyl)-2,3-dihydroquinazolin-4(1H)-one: Compound 3(0.01mol) dissolved in DMF. To this, equimolar quantities of primary or secondary amine (0.01mol) was added and refluxed for 2hrs. The mixture was cooled and poured into crushed ice. The separated solid was filtered, dried and re-crystallized.

TLC mobile phase: n-butanol: ethylacetate: benzene-1:2:1

Scheme of the present study

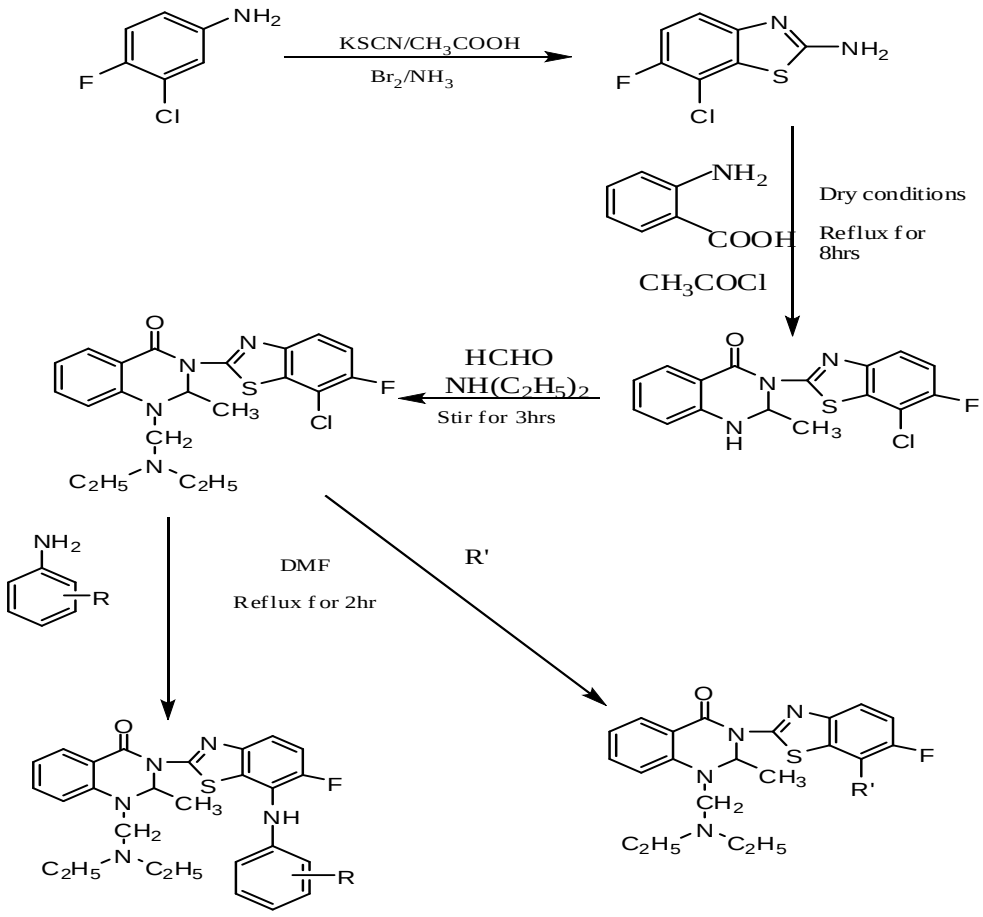

Table.1.Details of the synthesized compounds

Compound code	Amine
4a	o-Anisidine
4b	m-Anisidine
4c	p-Anisidine
4d	o-Toluidine
4e	m-Toluidine
4f	p-Toluidine
4g	β-phenylethylamine
4h	Morpholine

Table.2.Physical characterizations of the synthesized compounds

Compound	MOL. FORM	Mol. Wt	Rf value	M.P °C	% Yield	Elemental analysis (Calculated)		
						C	H	N
4a	$C_{28}H_{30}O_2SN_5F$	519	0.65	107	65%	59.82	4.05	13.42
4b	$C_{28}H_{30}O_2SN_5F$	519	0.64	108	67%	59.82	4.05	13.42
4c	$C_{28}H_{30}O_2SN_5F$	519	0.67	110	70%	59.82	4.05	13.42
4d	$C_{28}H_{30}OSN_5F$	503	0.71	160	68%	61.72	4.18	13.84
4e	$C_{28}H_{30}OSN_5F$	503	0.71	159	59%	61.72	4.18	13.84
4f	$C_{28}H_{30}OSN_5F$	503	0.73	162	69%	61.72	4.18	13.84
4g	$C_{28}H_{32}OSN_5F$	505	0.72	103	71%	62.36	4.46	13.47
4h	$C_{32}H_{38}O_4SN_5F$	607	0.69	96	69%	56.85	4.36	14.41

Spectral analysis: Compound 4a: IR (KBr, cm^{-1}): 3039.42(Ar-CH), 1306.11(Ar-NH), 1630(C=N), 1196(C-S). ^{1}H-NMR (DMSO, δ in ppm): 6.7-7.2(s, Ar-H, 11H), 2.97(m, N-CH_2, 3H), 8.43(s, $CONH_2$, 1H), 3.1(d, NH, 1H), 5.28(s, CH_3, 1H),

Compound 4d: IR (KBr, cm^{-1}): 3041.56(Ar-CH), 1229.11(Ar-NH), 1604(C=N), 1643(ArC=O), 1190(C-S). ^{1}H-NMR (DMSO, δ in ppm): 6.7-7.4(m, Ar-H, 11H), 3.8(s, O-CH_3, 3H), 8.43(s, $CONH_2$, 1H), 3.31(d, CH-H_B, 1H), 5.28(s, CH-Cl, 1H), 3.1(d, Ar-NH_2, 2H), 2.93(t, N-CH_2-C, 2H).
Compound 4h: IR (KBr, cm^{-1}): 3012.56(Ar-CH), 1356.3(Ar-NH), 1595(C=N), 1160(C-S). ^{1}H-NMR (DMSO, δ in ppm): 6.7-7.5(m, Ar-H, 11H), 4.1(s, N-H, 1H), 8.43(d, $CONH_2$, 1H), 2.97(m, N-CH_2, 4H)
Anti-microbial Screening (Venkatesh, 2009): The synthesized compounds were subjected to Antimicrobial screening by disc plate method for zone of inhibition. The anti-bacterial activity was tested against various Gram positive and Gram negative bacteria and anti-fungal activity against various fungal strains compared with standard drugs, Ciprofloxacin and Fluconazole using solvent control, DMSO. The results were described in Table.3 and 4.

Table No: 3 Antibacterial activity of the synthesized compounds

Compound	*Bacillus subtilis*		*S. aureus*		*K. pneumonia*		*Eschericia coli*	
	Concentration (µg/mL)							
	50	**100**	**50**	**100**	**50**	**100**	**50**	**100**
4a	11	13	7	10	7	8	11	13
4b	11	12	8	11	11	14	10	11
4c	10	11	6	8	8	11	11	13
4d	7	8	9	11	9	11	8	9
4e	11	12	8	10	7	10	7	9
4f	9	10	10	13	10	13	8	10
4g	12	9	11	12	11	13	11	12
4h	11	13	9	8	10	12	11	13
standard	13	15	11	13	12	15	13	16

Table no: 4 Antifungal activity of the synthesized compounds

Compound	Mean zone of inhibition (*in mm*)			
	Aspergillus flavus		*Aspergillus niger*	
	150µg/ml	200µg/ml	150µg/ml	200µg/ml
4a	11	12	10	12
4b	6	8	4	7
4c	7	12	8	14
4d	7	8	6	10
4e	8	11	6	11
4f	9	10	9	12
4g	7	11	8	12
4h	10	12	9	13
Fluconazole	11	13	15	17
Control	6	9	7	10

3. RESULTS AND DISCUSSION

All the synthesized compounds were first purified by successive recrystallisation using appropriate solvents. The synthesized compounds were characterized, subjected to spectral analysis such as IR, ^{1}H-NMR and were screened for anti-microbial activities. Out of these synthesized compounds, 4a and 4h showed significant activity and others showed moderate activity over biological activities.

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