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Design and Synthesis of Some Heterocyclic Compounds as Potential Antimicrobial Agents

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Abstract - A series of 3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(arylidene) thiazolidin-4-one (5a-i) have been synthesised as a potent antimicrobial agents. The precursor 3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl) thiazolidin-4-one (4) (Knoevenagel adduct) is synthesized by treatment with *N*-(benzo[*d*]thiazol-2-yl)-1-(2-chloroquinolin-3-yl) methanimine (3) and TGA (2) in rectified spirit. All synthetic steps were designed by green procedure with optimization of yields. Product obtained were characterised by means of the NMR, IR and Mass spectral techniques. All the synthesized compounds were evaluated for their *in-vitro* antimicrobial activity against various bacterial and fungal strains using Ketoconazole and Ciprofloxacin as a standard.

Keywords: Quioline, Benzo [*d*]thiazol-2-amine, Knoevenagel reaction, Green synthesis.

I. Introduction

The concern in biology, pharmacology, optics, electronics, material sciences, the various types of hetero particles of aromatic organic compounds are occur. [1,2]. The concern of researchers during decades of historical growth of organic synthesis, the sulphur and nitrogen containing five and six member heterocyclic compounds have maintained.

The pattern of novel medicines and substances, the sulphur-nitrogen aromatic heterocyclic compounds display physicochemical properties with significance. They relating to molecular conductors and magnets. Throughout the beyond many years, interest has been fast

developing in increasing nearby into the properties and alterations and establish attractive characteristics they are in the progressive synthetic system.

The reaction of alkyl di-isopropylamines with disulphurdichloride, which is able to give several different heterocyclic structures, depending on the reaction conditions [3]. In synthesis of condensed triazole heterocycles, some heterocycles have been found to possess many unique properties and have attracted a huge deal of attention from chemists and pharmacologists because of their broad spectra of biological activities such as microbial and many more activities. [4-6], There are many reports [7-10] on the synthesis of triazolo [3,4-*b*][l,3,4]thiadiazole derivatives.

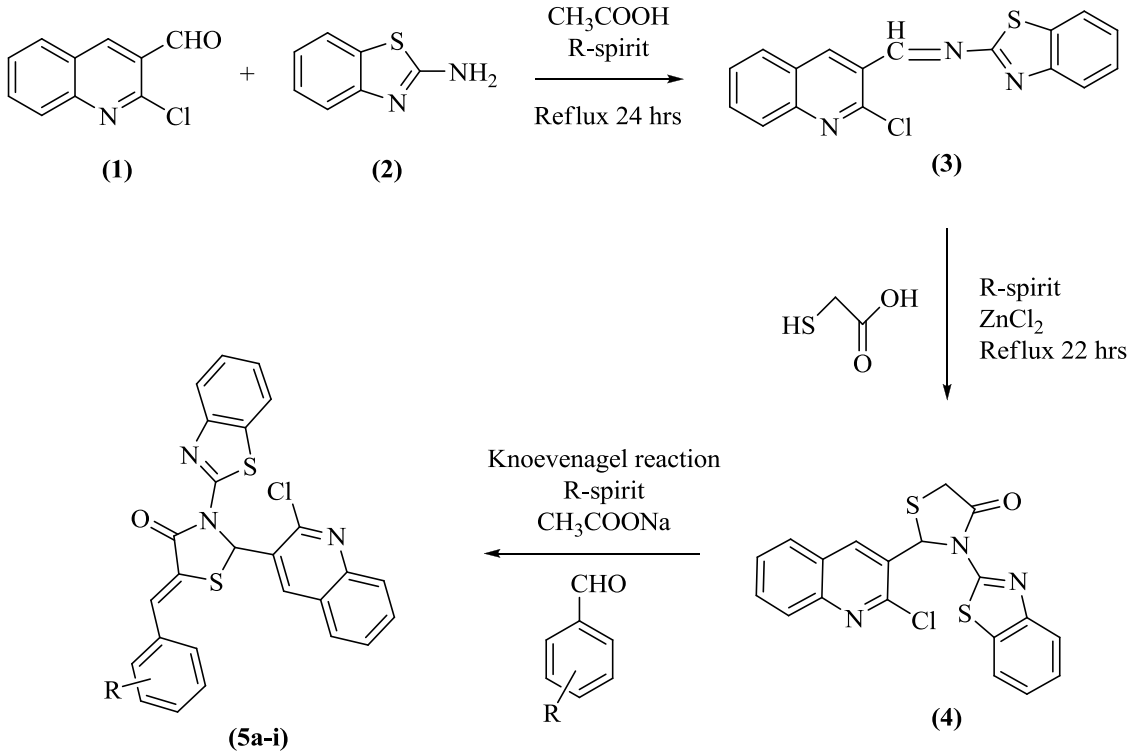
II. Experimental

2.1. Materials and methods

The required chemicals were purchased from E. Merck. Melting points were recorded on Gallenkamp apparatus and were left uncorrected. The completion of reaction and the purity of all compounds was checked on aluminum-coated TLC plates 60, F_{245} (E. Merck) using various solvent systems as mobile phase and visualized under ultraviolet (UV) light, or iodine vapor. Elemental analysis (% C, H, N) was carried out by a Perkin-Elmer 2400 CHN analyzer. IR spectra were also recorded on Perkin Elmer FT-IR spectrophotometer. ^{1}H NMR and spectra were recorded on Varian Gemini 400 MHz in $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer.

2.2. Procedure for the preparation.

Take an equivalent mixture of 2-chloroquinoline-3-carbaldehyde **(1)** (1 mol) and benzo [*d*]thiazol-2-amine **(2)** (1.2 mol) were placed in a three-necked round bottom flask equipped with a mechanical stirrer at 90°C for 24 hr by adding acetic acid in ethanol (1:2) (20 mL). After completion of reaction monitored by TLC, the precipitate crystallized solid was separate out which, re-crystallized from methanol to obtain pure compound, N-(benzo[*d*]thiazol-2-yl)-1-(2-chloroquinolin-3-yl) methanimine **(3)**. In next step, compound **(3)** and 2-mercaptoacetic acid with pinch of zinc chloride was charged in 100 mL RBF in R-spirit (10 mL) stir for 22 hr at 120°C. After the completion of the reaction was confirmed by TLC, solid mass separated was collected by filtration and easy isolation and re-crystallized with methanol to obtain compound 3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)thiazolidin-4-one **(4)**. In last step, different R-substituted aldehyde and sodium acetate were plucked in 100 mL RBF with compound **(4)** in R-spirit (10 mL) to give Knoevenagel adducts **(5a-i)** stir for 6 to 8 hr at 90°C. Completion of the reaction were confirmed by TLC obtained solid mass separated by filtration, dried and re-crystallized with methanol. The products were received quantitatively (80-94% yield) with good purity.



Reaction pathway for the synthesis of 5a-i

3-(benzo [*d*]thiazol-2-yl)-5-benzylidene-2-(2-chloroquinolin-3-yl) thiazolidin-4-one (5a)

$C_{20}H_{16}ClN_3OS_2$; M.W. 486.00 g/mole; Elemental Analysis: C, 64.26; H, 3.32; Cl, 7.29; N, 8.65; O, 3.29; S, 13.19; IR (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 1715 (C=O).^{1}H NMR (ppm): 2.32, 2.49, 2.66, 3.41, 3.44, 7.22, 7.32, 7.43, 7.45, 7.60, 7.77, 7.80, 7.84, 7.32, 7.94, 8.34. MS: *m/z*: 485.04 (100.0), 487.04 (32.0%), 486.05 (28.1%), 487.04 (9.0%), 488.04 (9.0%), 489.04 (2.9%), 487.05 (2.7%), 488.04 (2.5%), 486.04 (1.6%), 486.04 (1.1%), 487.05 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(4-zmethoxybenzylidene) thiazolidin-4-one (5b)

$C_{26}H_{18}ClN_3O_2S_2$; M.W. 516.30 g/mole; Elemental Analysis: C,62.84; H, 3.52; Cl, 6.87; N, 8.14; O, 6.20; S, 12.43; (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 1720 (C=O). ^{1}H NMR (ppm): 2.88, 3.81, 4.11, 6.06, 7.07, 7.14, 7.19, 7.33, 7.46, 7.53, 7.55, 7.62, 7.65, 7.76, 7.81, 7.88, 7.90, 7.91, 8.15, 8.32, 8.41, 8.52. MS; *m/z*: 515.05 (100.0%), 517.05 (32.0%), 516.06 (29.2%), 518.05 (9.3%), 517.05 (9.0%), 519.05 (2.9%), 517.06 (2.7%), 518.05 (2.6%), 516.05 (1.6%), 517.06 (1.4%), 516.05 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(2-hydroxybenzylidene) thiazolidin-4-one (5c)

$C_{26}H_{16}ClN_3O_2S_2$; M.W. 502.00 g/mole; Elemental Analysis: C, 62.21; H, 3.21; Cl, 7.06; N, 8.37; O, 6.37; S, 12.77; (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 1735 (C=O); 654 (C-Cl); 3625 (-OH). ^{1}H NMR (ppm): 3.98, 7.01, 7.17, 7.19, 7.35, 7.39, 7.44, 7.47, 7.49, 7.51, 7.53, 7.58, 7.65, 7.73, 7.84, 7.90, 7.99, 8.10, 8.24, 8.26; MS; *m/z*: 501.04 (100.0%), 503.03 (32.0%), 502.04 (28.1%), 503.03 (9.0%), 504.04 (9.0%), 505.03 (2.9%), 503.04 (2.7%), 504.04 (2.5%), 502.04 (1.6%), 502.03 (1.1%), 503.04 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(4-nitrobenzylidene) thiazolidin-4-one) (5d)

$C_{26}H_{15}ClN_4O_3S_2$; M.W. 531.63 g/mole; Elemental Analysis: C, 58.81; H, 2.85; Cl, 6.68; N, 10.55; O, 9.04; S, 12.08; (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 1535 (-NO_2); ^{1}H NMR (ppm): 2.49, 3.16, 3.35, 7.32, 7.53, 7.55, 7.62, 7.64, 8.15, 8.17, 8.35, 8.40, 8.42; MS; *m/z*: 530.03 (100.0%), 532.02 (32.0%), 531.03 (28.1%), 532.02 (9.0%), 533.03 (9.0%), 534.02 (2.9%), 532.03 (2.7%), 533.03 (2.5%), 531.03 (1.6%), 531.02 (1.5%), 532.03 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(3-nitrobenzylidene) thiazolidin-4-one (5e)

$C_{26}H_{15}ClN_4O_3S_2$; M.W. 531.63 g/mole; Elemental Analysis: C, 58.81; H, 2.85; Cl, 6.68; N, 10.55; O, 9.04; S, 12.08; (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 1515 (-NO_2); ^{1}H NMR (ppm): 1.73, 3.35, 7.87, 7.89, 7.91, 8.34, 8.52, 8.54, 8.69; MS; *m/z*: 530.03 (100.0%), 532.02 (32.0%), 531.03 (28.1%), 532.02 (9.0%), 533.03 (9.0%), 534.02 (2.9%), 532.03 (2.7%), 533.03 (2.5%), 531.03 (1.6%), 531.02 (1.5%), 532.03 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(3-hydroxybenzylidene) thiazolidin-4-one (5f)

$C_{26}H_{16}ClN_3O_2S_2$; M.W. 502.00 g/mole; Elemental Analysis: C, 62.21; H, 3.21; Cl, 7.06; N, 8.37; O, 6.37; S, 12.77; (ν_{max}, cm^{-1}): Ar-CH (3017); 1599 (C=N); 1567 (C=C); 3615 (OH); ^{1}H NMR (ppm): 2.32, 2.66, 2.77, 2.88, 3.34, 3.83, 6.91, 7.02, 7.14, 7.23, 7.31, 7.40, 7.57, 7.76, 7.87, 7.90, 7.99, 8.33, 8.43, 8.69, 9.34, 9.78; MS; *m/z*: 501.04 (100.0%), 503.03 (32.0%), 502.04 (28.1%), 503.03 (9.0%), 504.04 (9.0%), 505.03 (2.9%), 503.04 (2.7%), 504.04 (2.5%), 502.04 (1.6%), 502.03 (1.1%), 503.04 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(4-ethoxy-3-hydroxybenzylidene)-thiazolidin-4-one (5g)

$C_{28}H_{20}ClN_3O_3S_2$; M.W. 502.00 g/mole; Elemental Analysis: C, 61.59; H, 3.69; Cl, 6.49; N, 7.70; O, 8.79; S, 11.74 ; (ν_{max}, cm^{1}): ArCH (3017); 1599 (C=N); 1567 (C=C); 1520 (OH); 1650 (OCH_2CH_3); ^{1}H NMR (ppm): 3.36, 3.82, 4.18, 6.94, 7.00, 7.21, 7.30, 7.38, 7.52, 7.67, 7.69, 7.86, 7.96, 7.97, 8.03, 8.15, 8.16, 8.25, 8.60, 8.97, 9.27, 9.72, 10.13, 10.36, 10.37; MS; *m/z*: 545.06 (100.0%), 547.06 (32.0%), 546.07 (30.3%), 548.06 (9.7%), 547.06 (9.0%), 547.07 (4.4%), 549.06 (2.9%), 548.06 (2.7%), 546.06 (1.6%), 549.07 (1.4%), 546.06 (1.1%).

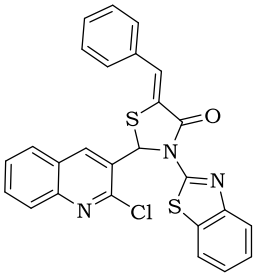
3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(2-hydroxy3methoxybenzylidene)-thiazolidin-4-one (5h)

$C_{27}H_{18}ClN_3O_3S_2$; M.W. 532.00 g/mole; ElementalAnalysis: C, 60.95; H, 3.41; Cl, 6.66; N, 7.90; O, 9.02; S, 12.05; (ν_{max}, cm^{1}): ArCH (3017); 1599 (C=N); 1567 (C=C); 1520 (OH); 1550 (OCH_3); ^{1}H NMR (ppm): 3.34, 3.84, 7.01, 7.24, 7.31, 7.43, 7.59, 7.76, 7.82, 7.84, 8.00, 8.05, 8.11, 8.33, 8.34, 8.41, 9.41, 9.63, 9.81; MS; *m/z*: 531.05 (100.0%), 533.04 (32.0%), 532.05 (29.2%), 534.05 (9.3%), 533.04 (4.5%), 533.04 (4.5%), 533.05 (4.1%), 535.04 (1.4%), 535.04 (1.4%), 534.05 (1.3%), 534.05 (1.3%), 535.05 (1.3%), 532.04 (1.1%).

3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(quinolin-3-ylmethylene) thiazolidin-4-one (5i)

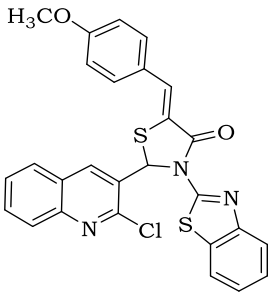
$C_{29}H_{17}ClN_4OS_2$; M.W. 537.07 g/mole; Elemental Analysis: C, 64.86; H, 3.19; Cl, 6.60; N, 10.43; O, 2.98; S, 11.94; (ν_{max}, cm^{1}): ArCH (3017); 1599 (C=N); 1567 (C=C); 1520 (OH); ^{1}H NMR (ppm): 2.32, 2.66, 3.41, 3.65, 7.16, 7.23, 7.31, 7.36, 7.39, 7.43, 7.48, 7.57, 7.59, 7.62, 7.64,

7.70, 7.74, 7.76, 7.91, 7.99, 8.01, 8.03, 8.28, 8.30 ,9.00, 10.38; MS; *m/z*: 536.05 (100.0%), 538.05 (32.0%), 537.06 (31.4%), 539.05 (10.0%), 538.05 (9.0%), 540.05 (2.9%), 539.05 (2.8%), 538.06 (2.7%), 538.06 (2.0%), 537.05 (1.6%), 537.05 (1.5%).



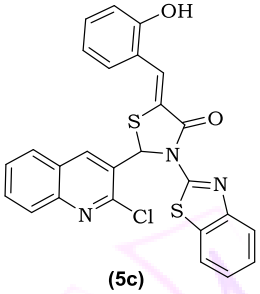
(5a)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-5-benzylidene-2-(2-chloroquinolin-3-yl)thiazolidin-4-one



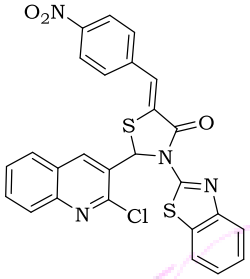
(5b)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(4-methoxybenzylidene)thiazolidin-4-one



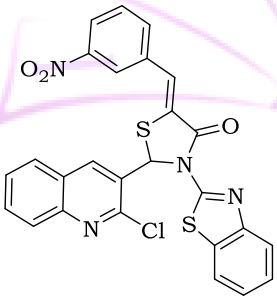
(5c)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(2-hydroxybenzylidene)thiazolidin-4-one



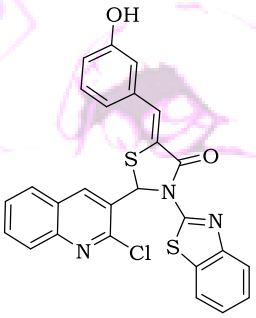
(5d)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)-5-(4-nitrobenzylidene)thiazolidin-4-one



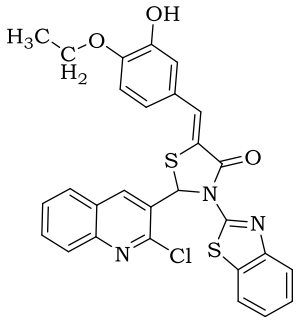
(5e)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl) -5-(3-nitrobenzylidene)thiazolidin-4-one



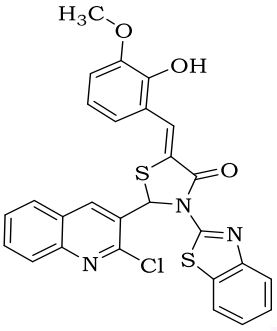
(5f)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl) -5-(3-hydroxybenzylidene)thiazolidin-4-one



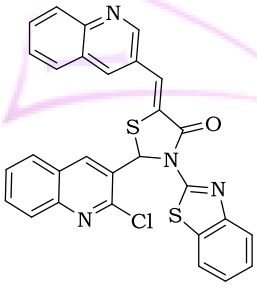
(5g)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)
-5-(4-ethoxy-3-hydroxybenzylidene)thiazolidin-4-one



(5h)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)
-5-(2-hydroxy-3-methoxybenzylidene)thiazolidin-4-one



(5i)

(*Z*)-3-(benzo[*d*]thiazol-2-yl)-2-(2-chloroquinolin-3-yl)
-5-(quinolin-3-ylmethylene)thiazolidin-4-one

III. Antibacterial Activity

The investigation of antimicrobial activity data **table**, we conclude that some compounds showed good to tremendous antibacterial activity against the illustrative specie compared to standard drugs. Against Gram-positive bacteria *B. subtilis*, and *C. tetani*, All compound prompted outstanding activity as compare to ciprofloxacin (MIC= 300 µg/mL) and comparable activity to that Ketoconazole.

Sample name (300 µg)	**Colour**	**Zones of growth inhibition in mm**					
		Gram Positive		**Gram Negative**		**Fungal Growth**	
		S. aureus	***B. subtilis***	***S. marcescens***	***E. coil***	***R. hizopus SP.***	***A. Niger (% inhibition)***
A	Brown	3.2	3.3	4.2	2.6	1.1	0.6(6%)
B	Light Brown	1.8	2.1	2.8	1.5	1.8	0.88(8%)
C	Light Brown	6.5	4.5	4.5	3.9	1.5	0.33(3%)
d	Light Brown	5.3	5	3.8	3.5	2..1	1.16(11 %)
e	Dark Brown	5.5	3.4	4.8	3.5	0.5	0.55(5%)
F	Brown	5.8	5.5	4.2	4.5	3.1	1.02(10 %)
G	Dark Brown	1.5	1.8	2.2	1.5	0.17	0.67(6%)
H	Light Brown	4.5	4.6	1.8	3.8	1.7	0.74(7%)
I	Brown	4.6	1.8	4.6	4.6	0.45	0.95(9%)
Control		0.1	0.1	0	0	0.1	0.1(1.1)
Ketoconazole		11.5	13.5	11.5	9.5	7.5	8.3(83%)
Ciproflox acin		12.8	11.4	12.5	10.5	8.5	7.6(76%)

IV. Conclusion

To develop a simple, eco-friendly and efficient method for synthesis, **of 3-(benzo[*d*]thiazol-2-yl)-5-benzylidene-2-(2-chloroquinolin-3-yl) thiazolidin-4-one** novel derivatives **(5a-i)**. This synthetic approach allows the integration of three auspicious bioactive nuclei in single scaffold through an easy way, for aiming their potent antimicrobial activities.

V. Acknowledgements

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VI. References

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