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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF N-ARYLQUINOXALIN-2-AMINES BEARING BENZIMIDAZOLE DERIVATIVES

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ABSTRACT: In the present study reports synthesis and development of 3-Chloro – N - ((5-chloro-1-tosyl-1*H*-benzo [d] imidazol – 2 - yl) methyl) - N arylquinoxalin-2-amines **(5a-e)** from 3-chloro-N-p-tolyl quinoxalin - 2-amine **(3)** condensed with proporgyl bromide followed by adding 4-chloro-N1-tosylbenzene-1,2-diamine,by adopting simple procedure. All titled compounds were screened for their anti bacterial activity by using bacterial strins i.e *Bacillus* subtilis MTCC 441, *Bacillus cereus* ATCC 9372, *E.coli* ATCC 8739, *and staphylococcus aureus* ATCC 96, compounds 5c, and 4c, were proven highest zone of inhibition against bacterial strains and 5b and 4b were also proven moderate inhibition zone against above mentioned bacterial strains, and the structures of synthesized compounds were characterized by ^{1}HNMR, ^{13}CNMR And Mass spectral data.

INTRODUCTION: In recent years, among the various classes of heterocyclic compounds, quinoxalines seemed as important component of pharmacologically active compounds. A quinoxaline, also called a benzopyrazine, in organic chemistry is a heterocyclic compound containing a ring complex made up of a benzene ring and a pyrazine ring. They are isomeric with quinozalines. Quinoxaline derivatives recently receive more attention of researchers [1-3]. Quinoxalines are an important class of nitrogen containing heterocycles with a variety of biological activities. In particular quinoxalines were found as a core unit in a number of biologically active compounds. These include anticancer [4, 5], antibacterial [6], antiviral [7], anti-inflammatory [8], anti HIV [9, 10] and anthelmintic activities [11].

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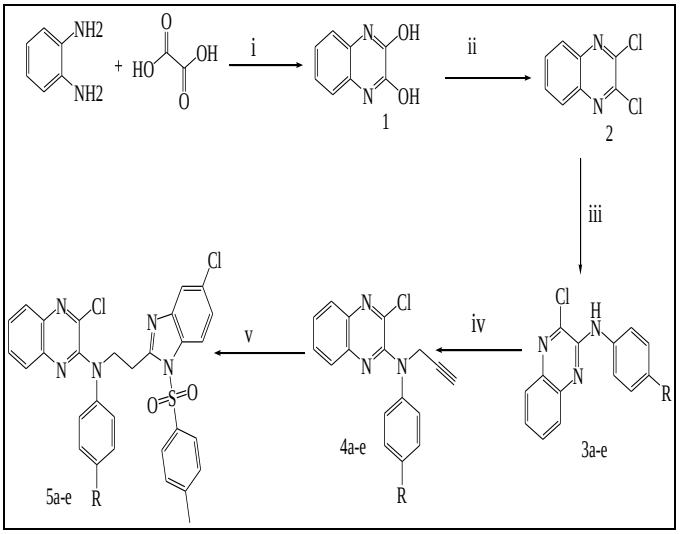
Among the various classes of nitrogen containing heterocyclic compounds, benzimidazoles and quinoxalines have been shown [12] to exhibit a wide range of biological and pharmacological properties. The benzimidazole derivatives have commercial application in veterinary medicine as anthelmintic agents [13] and in such diverse human therapeutic areas [14-17] as anti-ulcerous, anti-hypertensive, anti-viral, anti-fungal, anti-cancerous and antihistaminic agents. In view of the importance of the quinoxolines, we undertook the synthesis of these title compounds.

MATERIALS AND METHODS:

The ^{1}H NMR and ^{13}C spectra were recorded in the indicated solvent on a Varian 400 MHz and 200 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. The mass spectra were measured on a GC/MS-QP1000EX (EI, 70 eV) mass spectrometer. Column chromatography was performed on silica gel (Merck 60-120 mesh). All compounds were recrystalised from ethylacetate.

Experimental Section:

Scheme:



i) 4NHCl, Refluxed 1 hr **(ii)** $POCl_3$,stirred 1 hr**(iii)** aryl amine, EtOH ,reflux for 5 hr **(iv)** proporgyl bromide, Na_2CO_3,ethanol ,refluxed for 4-5 hr **(v)**4-chloro-N1-tosylbenzene-1,2-diamine, DCM,$Co_2(CO)_8$,stirring at RT for 2hrs

TABLE 1:

Compound	R
4a	CH_3
4b	OCH_3
4c	Br
4d	Cl
4e	F

TABLE 2:

Compound	R
5a	CH_3
5b	OCH_3
5c	Br
5d	Cl
5e	F

Synthesis of quinoxalin-2, 3-dione (1)

To a mixture of o-Phenylene diamine (0.25mole) and oxalic acid (0.36mole) 4NHCl (150ml) was added and refluxed in an oil bath for 1 hr and cooled. The crude solid that separated out was filtered, washed and recrystallised from ethanol.

Synthesis of 2, 3-dichloroquinoxaline (2)

Equimolar mixture of quinoxalin-2, 3-dione **1** (0.10mole) was treated with Phosphorous oxychloride (0.10mole) at room temperature and allowed to stand for 1 hr. The resultant product obtained was recrystallised from ethanol.

Synthesis of 3 – chloro – N – p – tolylquinoxalin - 2 -amine (3a-e)

A mixture of 2, 3-dichloroquinoxaline (0.01 mmol) and aryl amine (0.015 mmol) in EtOH (5 ml) was heated under reflux for 5 hr. After completion of the reaction, the reaction mixture was cooled at room temperature and ethanol was removed under reduced pressure. The resulting solid was washed with water and dried to afford the desired products **3(a-e)**.

Synthesis of 3-Chloro-N-aryl-N-(prop-2-ynyl) quinoxalin-2-amines (4a-e)

To a stirred solution of amine **(3)** (1 m mole) in ethanol (10 ml), proporgyl bromide (2.5 m mole) and Na_2CO_3 (2.5 m mole) were added and refluxed for 4-5 hr at 60^{o}C. After the completion of reaction, solvent was evaporated in vacuum and added water. The product was extracted from ethyl acetate.

3-Chloro-N-(prop-2-ynyl)-N- p – tolylquinoxalin – 2 - amine (4a)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.95 (d, 1H, J= 7.8 Hz), 7.88 (d, 1H, J= 7.8 Hz), 7.67 (t, 1H), 7.56 (t, 1H), 7.17 (d, 1H, J= 7.6 Hz), 7.03 (d, 1H, J= 7.6 Hz), 4.73 (d, 2H, J= 2 Hz), 2.37 (s, 3H), 2.19 (t, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149, 142, 141, 139, 138, 136, 130, 129, 127, 127, 127, 125, 79, 72, 43, 21.

Mass: m/z=308.6 [M+^{1}]

3 - Chloro - N - (4-methoxyphenyl) – N - (prop - 2-ynyl) quinoxalin-2-amine (4b)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.92 (d, 1H, J= 7.8 Hz), 7.90 (d, 1H, J= 7.8 Hz), 7.67 (t, 1H), 7.54 (t, 1H), 7.09 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 4.69 (d, 2H, J= 2.4 Hz), 3.82 (s, 3H), 2.19 (t, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158, 149, 141, 139, 138, 138, 130, 127, 127, 127, 114, 79, 72, 72, 55, 55, 43.

Mass: m/z=325 [M+1]$^+$

3 - Chloro- N - (4-bromophenyl)-N-(prop-2-ynyl) quinoxalin-2-amine (4c)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.94 (d, 1H), 7.91 (d, 1H), 7.72 (t, 1H), 7.62 (t, 1H), 7.49 (d, 2H), 7.01 (d, 2H), 4.74 (d, 2H, J= 2 Hz), 2.21 (t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148, 144, 141,

139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43.

Mass: m/z=374 $[M+1]^+$

3-Chloro – N - (4-chlorophenyl)-N-(prop–2-ynyl) quinoxalin-2-amine (4d)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.93 (d, 1H), 7.90 (d, 1H), 7.72 (t, 1H), 7.61(t, 1H), 7.48 (d, 2H), 7.00 (d, 2H), 4.73 (d, 2H, J= 2.2 Hz), 2.20 (t, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 148, 144, 141, 139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43.

Mass: m/z=329 $[M+1]^+$

3-Chloro-N-(4-fluorophenyl)–N-(prop – 2 - ynyl) quinoxalin-2-amine (4e)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.93 (d, 1H), 7.90 (d, 1H), 7.70 (t, 1H), 7.60 (t, 1H), 7.50 (d, 2H), 7.00 (d, 2H), 4.73 (d, 2H, J= 2 Hz), 2.20 (t, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 149, 144, 141, 139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43.

Mass: m/z=313 $[M+^1]$

3 - Chloro – N - (2 - (5-chloro – 1 – tosyl – 1 *H* - benzo[d]imidazol-2-yl) ethyl) -N-arylquinoxalin-2-amines (5a-e)

To a solution of compound **3a** (1 m mole) in DCM (30 ml), $Co_2(CO)_8$ (1.2 m mole) was added at RT. After stirring at RT for 2hrs, solvent was removed. To the above crude product in toluene (50 ml) DMSO (20 ml) was added and refluxed for overnight at 80^{o}C. After the completion of reaction, it was extracted with DCM, dried and concentrated to get the product.

3-Chloro - N - (2(5-chloro - 1 - tosyl - 1H - benzo [d] imidazol-2-yl) ethyl)-N-p-tolylquinoxalin-2-amine (5a)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.87 (d, 1H), 7.84 (d, 1H), 7.79 (d, 1H), 7.65 (m, 3H), 7.62 (d, 1H), 7.55 (m, 1H), 7.14-7.01 (m, 7H), 4.56 (t, 2H), 3.62 (t, 2H), 2.50 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161, 159, 151, 149, 145, 142, 141, 139, 139, 139, 135, 135, 133, 129, 127, 127, 126, 126, 126, 126, 125, 119, 116, 113, 52, 27, 21, 21.

Mass: m/z=604 $[M+1]^+$

3-Chloro-N- (2 - (5 – chloro -1-tosyl-1H-benzo[d] imidazol – 2 - yl) ethyl) – N - (4methoxyphenyl) quinoxalin-2-amine (5b)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.91 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.69 (m, 3H), 7.60 (d, 1H), 7.56 (m, 1H), 7.18-7.02 (m, 7H), 4.58 (t, 2H), 3.77 (s, 3H), 3.61 (t, 2H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161, 159, 151, 149, 145, 142, 141, 139, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 45, 27, 21.

Mass: m/z=620 [M+1]

3-Chloro – N - (2-(5-chloro-1-tosyl - 1H - benzo [d] imidazol – 2 -yl) ethyl) – N - (4-bromophenyl) quinoxalin-2-amine (5c)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.95 (d, 1H), 7.91 (d, 1H), 7.79 (d, 1H), 7.70 (m, 3H), 7.65 (d, 1H), 7.58 (m, 1H), 7.49 (d, 2H), 7.20-7.01 (m, 5H), 4.56 (t, 2H), 3.62 (t, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160, 159, 151, 149, 145, 142, 141, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21.

Mass: m/z=668 $[M+1]^+$

3 - Chloro - N - (2 - (5 - chloro - 1 - tosyl - 1H - benzo[d] imidazol-2-yl) ethyl)-N-(4chlorophenyl) quinoxalin -2-amine (5d)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.96 (d, 1H), 7.91 (d, 1H), 7.80 (d, 1H), 7.69 (m, 3H), 7.66 (d, 1H), 7.59 (m, 1H), 7.49 (d, 2H), 7.19-7.02 (m, 5H), 4.51 (t, 2H), 3.61 (t, 2H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160, 159, 151, 149, 145, 142, 141, 141, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21.

Mass: m/z=624 $[M+1]^+$

3 - Chloro – N - (2- (5 – chloro – 1 - tosyl - 1H – benzo [d] imidazol – 2 - ylmethyl) – N - (4 - fluorophenyl) quinoxalin-2-amine (5e)

^{1}HNMR (400MHz $CDCl_3$): δ = 7.94 (d, 1H), 7.90 (d, 1H), 7.81 (d, 1H), 7.70 (m, 3H), 7.65 (d, 1H), 7.60 (m, 1H), 7.50 (d, 2H), 7.21-7.03 (m, 5H), 4.52 (t, 2H), 3.63 (t, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160, 159, 151, 149, 145, 142, 141, 141, 139, 139, 138, 135, 134, 133, 130, 127,

127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21.

Mass: m/z=607 $[M+1]^+$

Antibacterial activity:

Bacterial Cultures:

Strains of Bacillus subtilis MTCC 441, Bacillus cereus ATCC 9372, *Staphylococcus aureus* ATCC 96, *E. coli* ATCC 8739, were taken from Department of Microbiology, Kakatiya University Warangal. The bacterial cultures were developed by selective nutrient broth at 37°C and stored at 4°C for further use.

Preparation of sample/test solution for antibacterial activity:

The Antibacterial activity testing of the selected cultures was carried out according to the method described by Raman [18]. Each selective medium was inoculated with the microorganism suspended in nutrient broth. Once the agar was solidified, it was punched with the wells of 6 millimeters diameter and was filled with 25 µl of the plants extract and some were kept as blanks (sterilized distilled water). Gentamycin sulfate were used as positive control was sterile distilled water. The plates were incubated at 35 ± 2°C for 24 hrs and the antimicrobial activity was observed and calculated.

TABLE 3:

compounds	*B.subtitis*	*B.cereus*	*E.coli*	*S.aureus*
4a	9	11	12	7
4b	5	7	12	11
4c	10	11	13	15
4d	5	4	6	5
4e	3	2	4	3
5a	8	10	16	8
5b	7	8	14	9
5c	12	14	18	17
5d	6	5	7	7
5e	4	4	3	4

RESULTS:

The synthesized compounds evaluated for antibacterial activity reveled notable activity. Among, the bacterial strains tested gram negative spices are more susceptible than the gram positive strains. According to the results obtained in this study it is clear that Cl and Br containing derivatives are more active against *E.coli* and *Staphylococcus aureus*. The highest zone of inhibition was noticed against *E.coli* (18mm) and *Staphylococcus aureus* (17mm) towards compound 5c.

On the other hand compound 4c was also exhibited significance antibacterial activity against *E.coli* and *Staphylococcus aureus* with zone of inhibition 13 and 15 respectively. Comparing to gram negative strains, gram positive strains to the compounds tested. This is might be caused of variations in the composition of bacterial cell wall. As gram negative bacterial cell wall is very thin the break down and lyses easily associated compound to gram positive bacterial cell wall.

The descending order of the compounds with antibacterial activity follows

5c>4c>5b>4b>5a>4a>5d>4d>5e>4e

RESULTS AND DISCUSSION:

In the view of the present study, we have efficiently synthesized N-arylquinoxalin-2-amines containing some new type of benzimidazole derivatives and which were screened for their antibacterial activity. Our Efforts was mainly focused on the synthesis and development of some new type of 3-Chloro-N-((5 - chloro - 1 - tosyl - 1 *H* - benzo [d] imidazol - 2 -yl)methyl)-N-arylquinoxalin-2-amines **(5a-e)** from compound (4) by using 4-chloro-N-1-tosylbenzene-1, 2-diamine by adopting simple procedure. Among the synthesized compounds 5c, 4c, 5b, 4b were exhibit significant antibacterial activity against standard drug. And all synthesized compounds were characterized by elemental analysis, ^{1}HNMR, ^{13}CNMR and Mass spectral data.

CONCLUSION: The present study reports an efficient synthesis of title compounds in good yields and moderate to potent antibacterial activities.

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