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SYNTHESIS AND BIOLOGICAL ACTIVITY STUDIES OF QUINOXALINE DERIVATIVES

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Abstract:-Various quinaoxalines were synthesized by the 1,2-diamines was the key intermediate for the synthesis of the new quinoxaline analogues, as it was appropriately substituted with various amines using tetra hydro furan as base in dimethylsulfoxide afforded a series of novel quinoxaline derivatives in good yields. The structures of all the newly synthesized molecules were assigned by spectral data. The synthesized compounds were screened for their antibacterial activities strains using Cup–Plate method.
Keywords: 2-Hydroxy-1-phenylethanone, tetra hydro furan, anti-bacterial activity.

Introduction

Quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals and microorganisms. The first quinazolinone was synthesized[i] in the late 1860's from anthranilic acid and cyanogens to give 2-cyanoquinazolinone. Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950's with the elucidation of a quinazolinone alkaloid, 3-[b-keto-g-(3-hydroxy-2-piperidyl)- propyl]-4-quinazolone febrifugine[ii], from an Asian plant Dichroa febrifuga, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria [iii-vii].

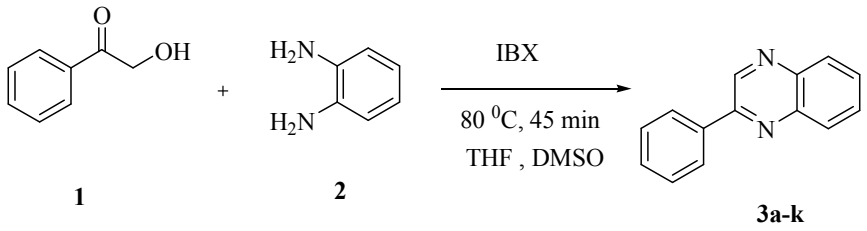
More recently within the past decade, *o*-iodoxybenzoic acid (IBX), the precursor of Dess–Martinv[iii,ix] periodinane, has seen a dramatic increase in use as a reagent, despite its first description having been published over a century ago (1893). In connection with our recent interests aimed at the development of efficient protocols for the preparation of biological active quinoxaline[x] derivatives we herein report an efficient method for the synthesis of quinoxaline derivatives. In this methodology IBX is used as an efficient oxidizing agent in the oxidation and condensation reaction of 2-hydroxy-1-phenylethanone **(1)** with 1,2-diamines **(2)** leading to formation of quinoxaline derivatives in THF and 1 drop of DMSO at 80 °C for 45 min. Having established the reaction conditions[xi-xv], various hydroxyl ketones were subjected to react with diamines in order to investigate the reaction scope and several representative results are illustrated in **(Table-1).**

Results and discussions

Chemistry

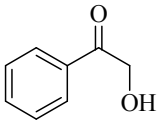
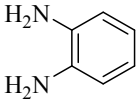
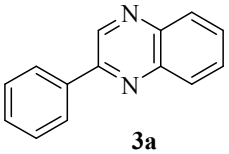
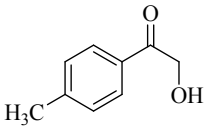
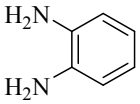
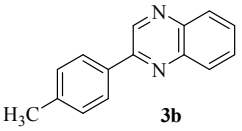
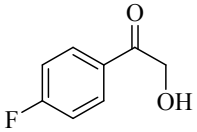
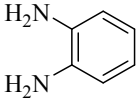
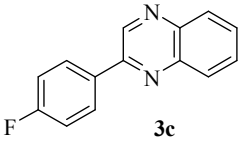
We have successfully synthesized nine novel compounds **(3a-k)** in good yields via 1,2-diamines **(2)** by employing the reaction sequences shown in (**Scheme-2**).

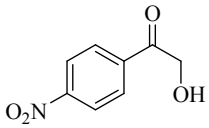
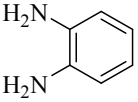
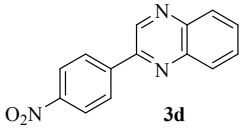
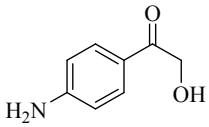
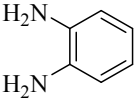
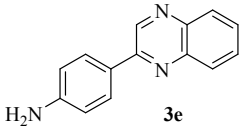
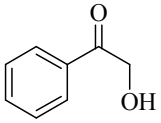
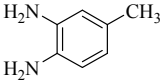
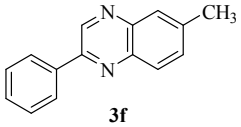
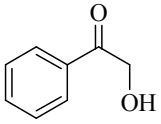
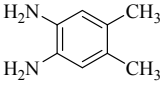
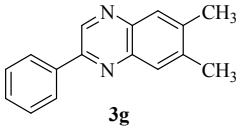
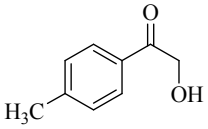
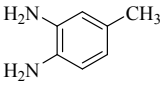
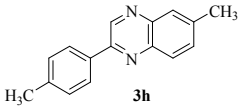
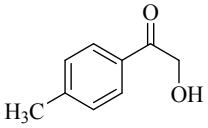
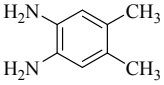
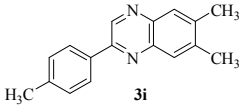
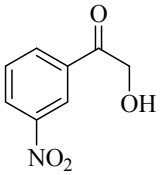
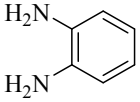
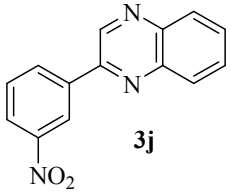
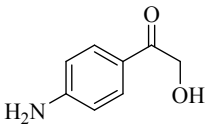
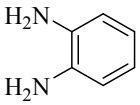
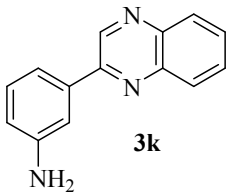
Attempts for the oxidative cyclization of 2-hydroxyacetophenone (**1**) with *o*-phenylenediamine **2** carried out in presence of IBX at 80 °C in THF-DMSO (9:1) to give quinoxaline **3**. The IBX catalyzed synthesis of quinoxalines from the reactions between 2-hydroxy-1-phenylethanone **(1)** with 1,2-diamines **(2)** the oxidative cyclized products (**3a-k**) were formed in the range of 80-97% of yields without any identifiable side product (Table 1). The product yield was not significantly affected by the position of the substituent on the aromatic ring of either hydroxyl ketone or diamine, whereas the electronic nature of that had some relevance to the product yield. The ^{1}H NMR (300 MHz, $CDC1_3$) spectrum of compound **3a** appeared ð 7.61-7.40 (m, 3H, Ar-H), 7.82-7.66 (m, 2H, Ar-H), 8.16-8.06 (m, 2H, Ar-H), 8.25-8.17 (m, 2H, Ar-H), 9.31 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDC1_3$) ð (ppm) 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2,143.3, 151.7; MS (ESI) *m/z* 207 $(M+H)^+$.



1 **2** **3a-k**

Scheme 1: Synthesis of title compounds quinoxalines (3a-k)

S.No	Hydroxy Ketone	1,2 Diamine	Product	Time (min)	Yield %
1	 **1a**	 **2a**	 **3a**	45	95
2	 **1b**	 **2a**	 **3b**	40	95
3	 **1c**	 **2a**	 **3c**	40	90

4	 **1d**	 **2a**	 **3d**	50	85
5	 **1e**	 **2a**	 **3e**	45	90
6	 **1a**	 **2b**	 **3f**	40	96
7	 **1a**	 **2c**	 **3g**	40	98
8	 **1b**	 **2b**	 **3h**	40	93
9	 **1b**	 **2c**	 **3i**	40	97
10	 **1f**	 **2a**	 **3j**	45	80
11	 **1e**	 **2a**	 **3k**	40	97

Antibacterial activity:

All the newly prepared compounds **(3a-k)** were screened for the antibacterial activity is done by the paper disc method[xvi-xix]. Organisms used: Escherichia coli (gram-negative) Staphylococcus aureus (gram-positive)

After solidification of media, petriplates inoculated with actively growing culture of Escherichia coli and Staphylococcus aureus separately as follows. Filter paper discs of 5 mm diameter were dipped in the test solution of different concentrations. After drying the disc, it was kept on antibiotic med-3 agar in petriplates seeded with 1 ml bacterial culture of Escherichia coli and Staphylococcus aureus and incubated for 24 h at 37 °C.

The antibacterial screening data showed that almost all the compounds **3a-k,** are active and showing moderate to good antibacterial activity. Among the screened **3b**, **3e, 3f, 3g,** and **3i** in which respectively showed high activity against all the micro-organism employed. The activities of these compounds are almost equal to the standards the remaining compounds showed moderate to good antibacterial activity.

Table-i: Antibacterial activity

Escherichia coli (gram-negative) (Conc. µg ml^{-1})				**Staphylococcus aureus** (gram-positive) (Conc. µg ml^{-1})		
comp.	200	100	50	200	100	50
3**a**	22	21	-	12	21	9
3b	12	14	12	31	24	22
3c	11	13	8	-	14	7
3d	-	-	11	18	-	11
3e	18	19	30	28	19	23
3f	12	12	22	23	32	22
3g	23	19	17	11	19	17
3h	11	-	-	22	-	-
3i	22	11	17	13	11	17
3j	13	-	11	14	-	11
3k	14	11	11	26	29	19

Experimental section

General conditions

All the reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR ($CDCl_3$ 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass 70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

General procedure for the synthesis of compounds (3a-k)

Equimolar mixture of hydroxy ketone (**1a**, 136 mg, 1 mmol) and o-phenylenediamines **2a**, 108 mg,1 mmol) were heated in presence of IBX (420 mg, l.5 mmol) in THF:DMSO (9:1) at 80 °C for 45 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with EtOAc (l0 mL) and washed with brine (2 x 10mL), dried over anhydrous Na_2SO_4, and evaporated in *vacum*, and the resulting subjected to column chromatography on silica gel 5% with EtOAc in hexane and evaporation of solvent under reduced pressure gave pure product as milky white solid **3a** (196 mg, 95% yield). Mp 75-78 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð 7.61-7.40 (m, 3H, Ar-H), 7.82-7.66 (m, 2H, Ar-H), 8.16-8.06 (m, 2H, Ar-H), 8.25-8.17 (m, 2H, Ar-H), 9.31 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDC1_3$) ð 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2,143.3, 151.7; MS (ESI) *m/z* 207 $(M+H)^+$.

2-*p*-Tolylquinoxaline (3b)

Brown colour solid; mp 90-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (ppm) ð 2.45 (s, 3H, Ar-CH_3), 7.37-7.29 (m, 2H, Ar-H), 7.77-7.64 (m, 2H, Ar-H), 8.14-8.04 (m, 4H, Ar-H), 9.28 (s, 1H, Ar-H); ^{13}CNMR (75 MHz, $CDCl_3$) ð (ppm) 21.4, ;127.4, 129.0, 129.2, 129.5, 129.8, 130.1, 133.9, 140.4, 141.4, 142.2, 143.2, 151.7; MS (ESI) m/z: 220 $(M+H)^+$.

2-(4-Fluorophenyl) qninoxaline (3c)

Yellow color solid; mp: 120-122 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 7.18-7.28 (m, 2H, Ar-H), 7.67–7.82 (m, 2H, Ar-H), 8.06-8.12 (t, 2H, Ar-H), 8.18-8.27(m, 2H, Ar-H), 9.27 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDC1_3$) ð (ppm) 116.0, 116.3, 129.1, 129.4, 129.5, 129.5, 130.3, 132.9, 142.8, 150.6, 165.8; MS (ESI) *m/z* 225 $(M+H)^+$

2-(4-Nitro-phenyl)-quinoxaline (3d)

Yellow colour solid; mp 187-189 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 7.77-7.85 (m, 2H, Ar-H), 8.11-8.18 (m, 2H, Ar-H), 8.40 (s, 1H Ar-H), 9.36 (s, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDC1_3$) ð (ppm) 127.7, 128.4, 129.2, 130.8, 131.4, 133.0, 138.6, 142.8, 147.0, 149.1; MS (ESI) *m/z* 252 $(M+H)^+$.

4-Quinoxalin-2-yl-aniline (3e)

Black colour solid; mp 167-169 °C; ^{1}H NMR (500 MHz, $CDC1_3$) ð (ppm) 6.76 (dd, 1H, $J_{(l,2)}$ = 8.9, $J_{(1,3)}$ = 3.0, Ar-H), 7.29 (t, 1H, J = 7.9, Ar-H), 7.45-7.58 (m, 2H), 7.64-7.79 (m, 2H, Ar-H), 8.09 (t, 2H, J = 10.8, Ar-H), 9.25 (s, 1H, Ar-H) ^{13}CNMR (75 MHz, $CDC1_3$) ð (ppm) 113.7, 116.9, 117.6, 129.0, 129.3, 129.4, 129.9, 130.1, 137.7, 141.4, 142.1, 143.4, 147.2; MS (ESI) *m/z* 222 $(M+H)^+$.

6-Methyl-2-phenylquinoxaline (3f)

White color solid; mp 134-136 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 2.62 (s, 3H, Ar-CH_3), 7.61-7.42 (m, 4H, Ar-H), 8.03-7.82 (m, 2H, Ar-H), 8.18 (m, 2H, Ar-H), 9.24 (d, J = 7.3 MHz, 1H, Ar-H); ^{13}C NMR (75 MHz, CDC13) ð (ppm) 20.1, 127.2, 127.9, 128.4, 128.8, 129.6, 136.9, 139.9, 140.3, 140.6, 140.9, 142.2, 150.8; MS (ESI) *m/z* 220 $(M+H)^+$

6,7-DimethyI-2-phenylquinoxaline (3g)

Light yellow colour solid; mp 122-124 °C; ^{1}H (300 MHz, $CDC1_3$) ð (ppm) 2.51 (s, 6H, Ar-CH_3), 7.56–7.41 (m, 3H, Ar-H), 7.89 (m, 2H, Ar-H), 8.20-8.12 (m, 2H, Ar-H), 9.19 (s, 1H, Ar-H); ^{13}C NMR ($CDC1_3$, 75 MHz) ð (ppm) 20.3, 20.4, 127.3, 128.1, 128.6, 129.0, 129.8, 140.1, 140.8, 142.4; MS (ESI) *m/z* 234 $(M+H)^+$.

6-Methyl-2-p-tolylquinoxaline (3h)

Milky white color solid; mp 146-147 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 2.45 (s, 3H, Ar-CH_3), 2.61(s, 3H, Ar-CH_3), 7.31 (d, *J* = 8.3, 3H, Ar-H), 7.59-7.47 (m, 1H, Ar-H), 8.02-7.79 (m, 2H, Ar-H), 8.07 (d, 7 = 8.3, 2H, Ar-H), 9.22 (d, *J* = 7.5, 1H, Ar-H); ^{13}C NMR ($CDC1_3$, 75 MHz) ð (ppm) 21.3, 128.7, 129.1, 129.2, 129.3, 129.4, 130.3, 142.7, 142.8, 150.9; MS (ESI) *m/z* 234 $(M+H)^+$.

6,7-Dimethyl~2-p-tolylquinoxaline (3i)

Light brown color solid; mp 127-129 °C; ^{1}H NMR (300 MHz, $CDC1_3$): ð (ppm) 2.45 (s, 3H, Ar-CH_3), 2.51 (s, 6H, Ar-CH_3), 7.30 (d, *J* = 8.0, 2H, Ar-H), 7.82 (d, *J* = 9.5, 2H, Ar-H), 8.05 (d, *J* = 8.0, 2H, Ar-H), 9.17 (s, 1H, Ar H) ^{13}C NMR (75 MHz, $CDC1_3$) ð (ppm) 21.3, 22.9, 128.5, 129.0, 129.1, 129.3, 139.9, 141.3, 142.9, 151.9; MS (ESI) *m/z* 248 $(M+H)^+$.

2-(3-Nitrophenyl) quinoxaline (3j)

Light orange colour solid; mp 185-187 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 7.72-7.90 (m, 3H, Ar-H), 8.11-8.25 (m, 2H, Ar-H), 8.30 (t, 1H, $J_{(1,3)}$ = 8.3, $J_{(1,3)}$ =2.3, $J_{(1,3)}$ = 1.5, Ar-H), 8.6 (d, 1H, *J* = 8.3, Ar-H), 9.09-9.15 (m, 1H, Ar-H), 9.41(s, IH, Ar-H); ^{13}C NMR ($CDC1_3$, 75 MHz) ð (ppm) 122.5, 124.7, 129.2, 129.8, 130.2, 130.5, 130.9, 133.1, 142.5; MS (ESI) *m/z*: 252 $(M+H)^+$.

3-(Quinoxalin-2-yl)benzenamine (3k)

Yellow colour solid; mp 163-165 °C; ^{1}H NMR (300 MHz, $CDC1_3$) ð (ppm) 3.80 (bs, 2H, NH_2), 6.76 (dd, IH, $J_{(1,2)}$ = 2.9, $J_{(1,3)}$ = 8.9, Ar-H), 7.20-7.33 (m, IH, Ar-H), 7.45-7.59 (m, 2H, Ar-H), 7.64-7.80(m, 2H, Ar-H), 8.09 (s, 2H, *J* = 10.9, Ar-H), 9.25 (s, IH, Ar-H); ^{13}C NMR ($CDC1_3$, 75 MHz) ð (ppm) 113.8, 117.0, 129.1, 129.4, 129.5, 130.1, 130.2, 137.8, 141.6, 142.2, 143.5, 147.3, 152.0; MS (ESI) *m/z* :222 $(M+H)^+$.

Conclusion

We have successfully synthesized eleven novel quinoxalines **(3a-k)** via 2-hydroxyacetophenone (i) in good yields. We have developed by using IBX as an inexpensive, easy to handle, non-corrosive and environmentally benign catalyst for the synthesis of quinoxalines from aromatic *o*-diamines and hydroxy ketone compounds. The structures of all the compounds were confirmed by their spectral data.

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