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A green synthesis of quinoxaline derivatives & their biological actives

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Abstract

A simple and catalyst free synthetic method has been developed by the synthesis of quinoxaline derivatives from 2-chloro quinoxaline and different types of amine derivatives using PEG-400 green solvent at room temperature. This method is simple, ecofriendly, rapid-generates 2-amino quinoxaline derivatives and good yield without use any catalysts. PEG-400 increases the rate of reaction and reduces reaction time. Newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli, Bacillus subtilis, Pseudomonas, Staphylococcus aureus*. The structure of quinoxaline derivatives were confirmed by using IR, ^{1}H-NMR, Mass spectroscopy.

Keywords: 2-chloro quinoxaline, Catalyst free, Green synthesis, PEG-400.

INTRODUCTION:

Quinoxaline derivatives are an important class of heterocyclic compounds. It is rare in natural state, but their synthesis is easily to perform[1]. Quinoxaline molecular formula is $C_8N_2H_6$ and is formed by two aromatic rings, benzene and pyrazine. In quinoxaline pyrazine ring is water soluble and stable colourless compound. Benzene ring is fused with diazines compounds. The pyrazine ring system is present in the fungal metabolite aspergillic acid and also in luciferin. Methoxy pyrazine are essential component of aroma of many fruits and vegetables such as capsicum and peas[2].

In quinoxaline 6-membered nitrogen heterocyclies containing two nitrogens in

mutually para dispositions.These compounds have a wide range of applications in bacteriology, pharmacology and mycology[3-7,] Quinoxaline derivatives continued to be of great interest due to a wide spectrum of their biological activity such as actinolutin, echinomycin and levomycin that are know to inhibit growtth of gram positive bacteria[8-9], anti fungal[10-11], anti convulsant[12], anti depressant[13-14], anti neoplastic[15-17], anti viral[18], anti bacterial[19-21], anti inflammatory[22], anti malarial activity[23], anti HIV activity[24], quinoxaline derivatives are also used in dyes, organic semiconductor, cavitands and dehydroannulenes. Quinoxaline are important in industry also due to their ability to inhibit metal corrosion[25-27].

Polyethylene glycol-400[28], as an efficient reaction medium for preparation of quinoxaline derivatives containing nitrogen cyclic ring system. PEG-400 used in many organic reactions for conversion[29] of oxiranes to thiranes, asymmetric aldol reactions[30] in presence of L-Proline, cross-coupling reaction,[31] Baylis-Hillman reaction[32] and ring opening of epoxides.[33]

We now designed and synthesized a series of novel quinoxaline derivatives from 2-chloro quinoxaline by applying the principles of green chemistry using PEG-400 as an alternative reaction medium. PEG is an eco-friendly reaction solvent. PEG-400 is non-toxic, Inexpensive, potentially recyclable and water soluble, which facilitates it is easily removal from the reaction product.

EXPERIMENTAL:

All the chemicals were used as purchased from sigma-aldrich, Avra Laboratories. Solvents and reagents were obtained from commercial sources. Melting Points are uncorrected and were determined using open capillary tubes in sulfuric acid bath. TLC analyses were done on plastic sheets coated with silica gel G and spotting was done using Iodine/UV lamp. IR spectra were recorded on a Perkin Elmer model 1000 instrument in KBr Pellet. ^{1}H-NMR and ^{13}C NMR were recorded in $CDCl_3$/DMSO-d_6 using 400 MHZ and 100 MHz varian Gemini spectrometer and TMS as a reference standard. Mass spectra were recorded on an Agilent-LCMS instrument.

General procedure for the preparation of 4a :

A mixture of 3(10 mmol, 1eq), 6-Benzyl amino purine (10 mmol, 1eq), K_2CO_3(1.67g, 20mmol, 2eq), KI(0.3g, 3mmol, 0.3eq) and different solvent such as Acetonitrile/1,4Dioxane/THF/EToH/MeOH/DMF was heated at 80^0C-100^0C for 2-6 hr. The progress of reaction was monitored by TLC, after completion of reaction, mixture was diluted with water and extracted with E.A(2x25mL). The combined organic layer was washed with water, brine and then dried with anhydrous Na_2So_4. The organic layer was distilled under reduced pressure, gave respectively 4a(scheme

1, Table 1).

General procedure for the preparation of 4(a-j) under PEG-400 :

A Mixture of powderad anhydrous K_2CO_3 (1.67g, 20mmol, 2eq), PEG-400, KI(0.3g, 3mmol, 0.3eq) and 6-Benzyl amino purine/different amine derivatives (10 mmol, 1.0eq) was taken in a mortar and ground with a pestle for few minutes. To this mixture, starting material 3(10mmol, 1.0eq) was added and the whole mixture was ground with pestle in the mortar at room temperature. After sometime monitored by TLC after then, mixture was treated with ice-cold water(50 mL). product separated by filteration, washed with water, and dried to obtain products of 4(a-j) [scheme 1, Table 2].

Quinoxaline-2-ol: (2)

(^{1}H NMR (400 MHz, $CDCl_3$): 12.3ppm (s, 1H, Ar-OH), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 8.16(s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): (175.4, 142.4, 138.5, 135.4, 129.8, 128.6, 126.4, 122.5; LC-MS m/z, 147.19 $[M+H]^+$.

2-chloro quinoxaline: (3)

^{1}H NMR(400MHz, $CDCl_3$): 8.16 (s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t,1H, Ar-H), 7.91(d, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): (175.9, 143.5, 136.9, 133.4, 130.1, 127.6, 125.4, 123; LC-MS m/z, 165.59 $[M+H]^+$.

N-benzyl-N-(7H-purin-6-yl)quinoxalin-2-amine: (4a)

^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, Ar-H), 12.09(d, 1H, Ar-NH), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 4.24(s, 2H, CH_2), 7.16(d, 1H, Ar-H), 7.28(t, 1H, Ar-H), 7.20(t, 1H, Ar-H), 7.28(t, 1H, Ar-H), 7.16(d, 1H, Ar-H), 8.09(s, 1H, Ar-H), 8.21(d, 1H, Ar-H), ^{13}C NMR (100 MHz, $CDCl_3$) : (175.9, 164.5, 156, 152.7, 149, 138.7, 136.1, 133, 131.5, 130.6, 129.4, 127.3, 126.8, 126.2, 125.3, 124.9, 124, 123.2, 120.4, 59.1; LC-MS m/z, 354.14 $[M+H]^+$.

4-(quinoxalin-2-yl) morpholine: (4b)

^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.89(t, 2H, CH_2), 3.79(t, 2H, CH_2), 3.79(t, 2H, CH_2), 3.89(t, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) : 169.1, 142.3, 136, 132.4, 129.8, 127.4, 124.2, 121.6, 68.6, 68.6, 49.4, 49.4; LC-MS m/z, 216.11 $[M+H]^+$.

2-(piperidin-1-yl) quinoxaline: (4c)

^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.95(t, 2H, CH_2), 1.71(m, 2H, CH_2,), 1.83(m, 2H, CH_2), 1.71(m, 2H, CH_2), 3.95(t, 2H, CH_2); ^{13}C NMR (100 MHz,

$CDCl_3$): 169.1, 142.3, 136, 132.4, 129.8, 127.4, 124.2, 121.6, 55.3, 30.9, 27.4, 30.9, 55.3; LC-MS m/z, 214.13 $[M+H]^+$.

2-(piperazin-1-yl) quinoxaline: (4d)

^1H NMR(400 MHz, $CDCl_3$): 8.16 (s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.59(t, 2H, CH_2), 3.01(m, 2H, CH_2), 3.01(m, 2H, CH_2), 3.59(t, 2H, CH_2), 2.1(m, 1H, NH). ^{13}C NMR(100 MHz, $CDCl_3$): 169.1, 142.3, 136, 132.4, 129.8, 127.4, 124.2, 121.6, 53.9, 49.7, 49.7, 53.9. LC-MS m/z, 215.27 $[M+H]^+$.

2-(pyrrolidin-1-yl) quinoxaline: (4e)

^1H NMR(400 MHz, $CDCl_3$): 8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.07(t, 2H, HN-CH_2), 1.69(m, 2H, CH_2), 1.69(m, 2H, CH_2), 3.07(t, 2H, HN-CH_2); ^{13}C NMR(100 MHz, $CDCl_3$): 169.1, 142.3, 136, 132.4, 129.8, 127.4 124.2, 121.6, 60.1, 30.4, 30.4, 60.1; LC-MS m/z, 200.21 $[M+H]^+$.

2-(4-methylpiperazin-1-yl) quinoxaline: (4f)

^1H NMR(400 MHz, $CDCl_3$): 8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.91(t, 2H, CH_2), 2.58(t,2H, CH_2), 2.10(s, 3H, N-CH_3), 2.58(t, 2H, CH_2), 3.91(t, 2H, CH_2): ^{13}C NMR(100 MHz $CDCl_3$): 169.1, 142.3, 136.0, 132.4, 129.8, 127.4, 124.2, 121.6, 49, 58.7, 44.3, 58.7, 49; LC-MS m/z, 229.54 $[M+H]^+$.

N-benzylquinoxalin-2-amine: (4g)

^1H NMR(400 MHz, $CDCl_3$): 8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 4.27(t, 1H, Ar-NH), 4.52(d, 2H, N-CH_2), 7.14(d,1H, Ar-H), 7.49(t, 1H, Ar-H), 7.32(t, 1H, Ar-H), 7.49(t, 1H, Ar-H), 7.14(d, 1H, Ar-H); ^{13}C NMR(100 MHz $CDCl_3$): 169.1, 142.3, 136.0, 132.4, 129.8, 127.4, 124.2, 121.6, 50.1 142.6, 131.4, 132.7, 129.4, 132.7, 131.4; LC-MS m/z, 236.36 $[M+H]^+$.

N,N-diethylquinoxalin-2-amine: (4h)

^1H NMR(400MHz, $CDCl_3$):8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 3.97(m, 2H, N-CH_2), 1.35(t, 3H, CH_3), 1.35(t, 3H, CH_3), 3.97(m, 2H, N-CH_2); ^{13}C(100 MHz $CDCl_3$): 169.1, 142.3, 136, 132.4, 129.8, 127.44 124.2, 121.6, 43.4, 11.2, 11.2, 43.4; LC-MS m/z, 202.25 $[M+H]^+$.

N-butylquinoxaline-2-amine: (4i)

^1H NMR(400 MHz, CDCl3): 8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 4.9(t, 1H, NH), 3.6(m, 2H, CH_2), 1.71(m, 2H, CH_2), 1.43(m, 2H, CH_2), 1.09(t, 3H, CH_3); ^{13}C NMR(100 MHz $CDCl_3$): 169.1,

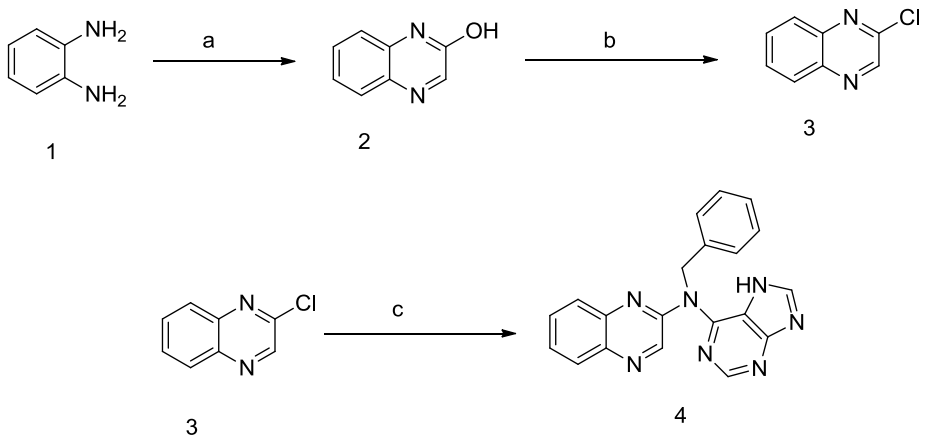
142.7, 136.0, 132.4, 129.8, 127.14, 124.2, 121.6, 49.2, 32, 23, 11; LC-MS m/z, 202.14 $[M+H]^+$.

N-(sec-butyl)quinoxaline-2-amine: (4j)

^{1}H NMR (400 MHz, $CDCl_3$): 8.16(s, 1H, Ar-H), 7.91(d, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.74(t, 1H, Ar-H), 7.91(d, 1H, Ar-H), 4.8(d, 1H, N-H), 1.21(d, 3H, CH_3), 2.84(m, 1H, N-CH), 1.65(m, 2H,-CH_2), 1.05(t, 3H, -CH_3); ^{13}C NMR(100 MHz, $CDCl_3$) : 162.9, 138.2, 137.1, 136.8, 129.1, 127.6, 126.4, 125.8, 53, 30.3, 20.7, 11.2; LC-MS m/z, 202.39 $[M+H]^+$.

RESULTS AND DISCUSSION:

O-Phenylene di amine (1) was treated with glyoxalic acid (50% H_2O) in presence of methanol at O^{o}C to obtain previously reported quinoxaline-2-ol[34-36] (2). Latter on treatment with $POCl_3$ in reflux condition for 3hr, followed by simple processing resulted in the formation of already reported 2-chloro quinoxaline[37-38] (3). The reaction of (3) with 6-Benzyl amino purine, K_2CO_3, and KI under refluxing different solvents such as Acetonitrile, DMF, 1,4-dioxane, MeOH, ETOH, THF, PEG-400, after then resulted in the formation of N-benzyl-N-(7H-purin-6-yl)quinoxalin-2-amine.

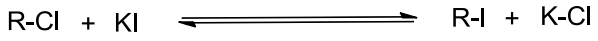


SCHEME-1

Reagents and conditions: a: glyoxalic acid(50% H_2O), MeOH, at 0^{o}C **b:** $POCl_3$ at reflux condition in 3hr, **c:** Acetonitrile, DMF, 1,4-Dioxane, MeOH, EtOH, THF, PEG-400, KI, K_2CO_3, 6-Benzyl amino purine.

Conversion of 3 to corresponding 4 is favored in presence of KI. This is probably due to the fact, that in presence of KI, chlorine of 3 is initially replaced by iodine and

subsequent reaction of iodine derivative of 3 with the nitrogen nucleophile is facile.

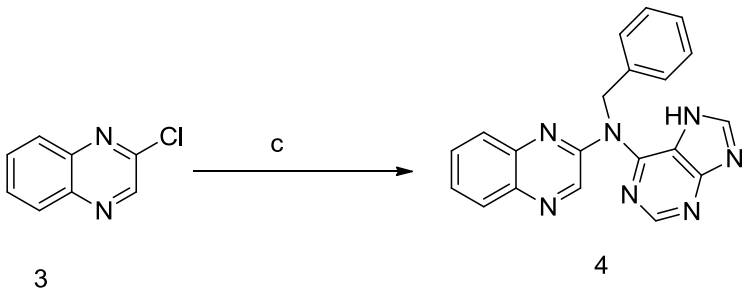


The reaction of (3) with 6-Benzyl amino purine in presence of different solvents and different reaction conditions, reaction is completed monitered by T.L.C and subsequent workup yielded product identical with one to each one, in all respects characterized by comparison with IR, mp Data. PEG-400 use as a solvent system, obtained good yield compared to remaining all solvent systems. We are found that above reactions between (3)and 6-Benzyl amino purine did not occur in the absence of PEG-400 even after grinding mixture of solids for 9-10 hrs. In this reaction PEG-400 act like a crown ether and the addition of KI, rate of reactivity increase because of PEG-400 enhances the neucleophilicity of the iodide ion and facilitating the reaction between 3 and 6-Benzyl amino purine.

TABLE-1 Effect of solvent on the reaction of 2-chloro-quinoxaline (3) with 6-Benzyl amino purine.

Entry	Solvent	Time/min.	Yield(%)[a]
1	Solvent-free	600	-
2	Acetonitrile	180	78
3	DMF	195	74
4	THF	205	83
5	1,4,Dioxane	200	85
6	MeOH	240	58
7	EtOH	225	64
8	PEG-400	35	94

All the reaction were performed using 3(1.0 mmol) and reactant in a solvent at room temperature under an open air condition. a isolated yield.



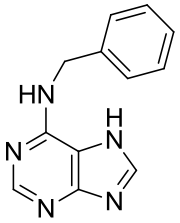
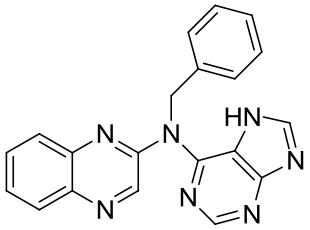
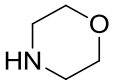
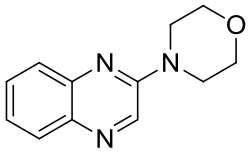
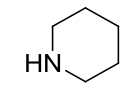
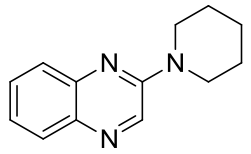
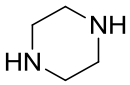
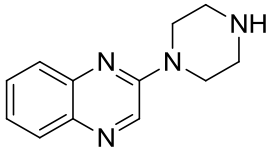
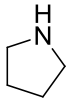
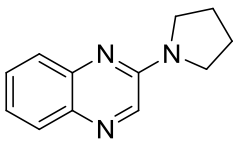
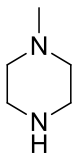
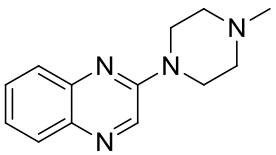
3 4

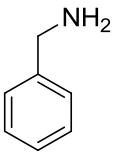
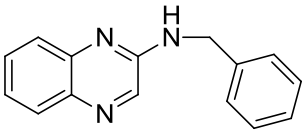
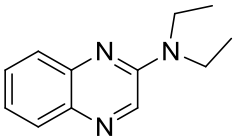
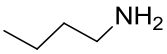
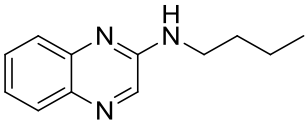
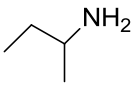
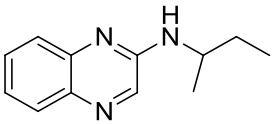
SCHEME-2

Reaction between 3 and 6-Benzyl amino purine in the presence of PEG-400 we obtained good yield and very less time reaction complete. PEG-400 has been found to

be a general one and has been extended to different nitrogen nucleophilic substrates such as 6-Benzyl amino purine, Isobutyl amine, Piperidine, Morpholine, pyrrolidine, Benzyl amine, Di ethylamine, Di methylamine, Piperazine, Methyl piperazine, n-Butyl amine.

TABLE-2: Preparation of quinoxaline derivatives in PEG-400 solvent

entry	Starting material	reactant	product	time/min.	Yield%
4a	3			45min.	86%
4b	3			25min.	94%
4c	3			30min.	92%
4d	3			40min	88%
4e	3			28min.	83%
4f	3			45min.	85%
					

entry	starting material	reactant	product	time/min.	Yield%
4g	3			70min.	75%
4h	3			35min.	80%
4i	3			78min.	85%
4j	3			85min.	89%

BIOLOGICAL ACTIVITY:

Newly synthesized compounds were screened for antibacterial activity study purpose micro-organisms employed were Gram positive (Bacillus.substillis, streptococcus.aureus), Gram negative (Escherichia. Coli, Pseudomonas.vulgaris).

TABLE-2: Antibacterial activity (Diameters in **mm** of zone of inhibition)

s.no	Product	E.Coli (mm)	Bacillus (mm)	S.aureus (mm)	Psedomonas (mm)
1	4a	26	28	22	19
2	4b	28	25	17	16
3	4c	20	18	14	12
4	4d	18	17	12	16
5	4e	14	12	10	10
6	4f	11	11	10	10
7	4g	13	10	11	10
8	4h	12	10	11	14
9	4i	11	16	14	15
10	4j	18	20	21	17

CONCLUSIONS

In summary, we have developed a simple and efficient method for preparation of new quinoxaline derivatives in solution phase and also under catalyst-free conditions using PEG-400 at room temperature. Present protocol has several advantages, particularly catalyst-free conditions, during work-up, water was used which is free from organic solvent, fast reaction times, high yields, eco-friendly operational and experimental simplicity, readily available catalyst.

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