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Design, Synthesis and Pharmacological Evaluation of Some Novel Quinoxalines Derivatives

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Diabetes and hyperlipidaemia are major risk factors for cardiovascular diseases on a global scale. It is common for patients with poorly controlled diabetes to have hyperlipidaemia. In the search for a novel class of antidiabetic and antihyperlipidemic medications, numerous compounds with a pyridine moiety have demonstrated good activity against diabetes and hyperlipidaemia. Developing, characterising, and screening quinoxaline derivatives for antidiabetic and antihyperlipidemic effects was the aim of the current study. The synthesised compounds were described using IR, MASS, 1H-NMR, and 13C-NMR spectroscopy. The synthesised compounds were tested for their antihyperlipidemic and antidiabetic effects in Swiss albino mice. Serum glucose, triglycerides, LDL (low-density lipoprotein), HDL (high-density lipoprotein), and total cholesterol levels in mice were measured using the blood sample. Comparable to the usual medication, the synthesised compounds 6a and 6d

exhibit good antidiabetic and antihyperlipidemic activity, which may be helpful for future clinical research.
Keywords: Quinoxaline, Spectral analysis, Diabetes, STZ.

1. Introduction

A high blood glucose level brought on by inadequate insulin activity is a hallmark of diabetes mellitus, a chronic metabolic disease (1). In 2023, there will be about 428 million persons with diabetes mellitus worldwide. The most prevalent causes of diabetes mellitus are oxidative stress, hyperglycemia, and hyperlipidaemia (2,3). Atherosclerosis and associated cardiovascular conditions, including peripheral vascular disorders, coronary heart disease, and ischaemic cerebrovascular disease, are all characterised by hyperlipidaemia. One of the main causes of illness and mortality in both India and the global population is cardiovascular disease.

It is responsible for over one-fourth of the nation's working-age mortality among those aged 25 to 65 (4). A survey carried out in various Indian states revealed that hyper-cholesterolemia is more common in urban areas than in rural ones, according to the Indian Council of Medical Research (ICMR) (5). High blood levels of lipids (fat, cholesterol, and triglycerides) are known as hyperlipidaemia (6). According to epidemiological research, the most common marker of atherosclerosis and heart disease risk is hyperlipidaemia. (7, 8) Consequently, lowering plasma lipid levels is crucial for both treating and preventing coronary heart disease. Because of this, a lot of research has been done to assess the potential lipid-lowering activity of synthetic, semisynthetic, and natural substances. One of the most prevalent side effects of diabetes mellitus is abnormalities in lipid profiles (9).

Triglycerides, LDL, VLDL, and cholesterol all rise when diabetes is induced. Serum lipid levels are often higher in people with diabetes mellitus, and this is a risk factor for coronary heart disease (10). The relationship between blood cholesterol levels and the risk of coronary heart disease (CHD) was first shown in 1984. The risk of CHD is lowered by 2% for every 1% decrease in serum cholesterol. However, the medications now in use are either not active enough or have undesirable side effects. While an increase in HDL may also be helpful in CHD, the major intended effect is still a decrease in LDL cholesterol content. Numerous investigations conducted in the past ten years have demonstrated the promising potential of pyrimidine derivatives as lipid-lowering medicines (11, 12). Targeting hyper-lipidemia with medication and/or dietary changes is a sensible way to prevent or treat atherosclerosis and lower the risk of cardiovascular disease events. In order to achieve this, attempts were made to create more potent and superior antihyperlipidemic medications. (13)

By substituting a nitrogen atom for the carbon atoms in the naphthalene ring, quinoxaline derivatives constitute a significant class of heterocyclic molecules. Quinoxaline is also known as benzopyrazine because it is composed of two rings: an aromatic benzene ring and a heterocyclic aromatic pyrazine ring. (14) It is known to be a bioisoster of benzothiophene, naphthalene, and quinoline. Quinoxaline is miscible with water and has a low melting point (M.P.) of 29–30 °C. Compared to the isomeric diazonapthalenes, quinazoline (pKa1.95), phthalazine (pKa3.47), and cinnoline (pKa2.42), it is significantly weaker due to its weak

basicity (pKa 0.56). Quinoxaline, a weekly basic bicyclic molecule composed of pyrazine and benzene, is a nitrogen-containing heterocycle. (15) Diazanaphthalene is another name for it. Quinazoline, phthalazine, and cinnoline are examples of naphthyridines, which are isomeric versions of quinoxaline. Its inclusion in biologically significant antibiotics like levomycin, actinoleutin, and echinomycin, which are effective against a number of transplantable tumours, demonstrates its diverse range of activity. (16) It has a broad range of biological actions, including anticancer, anti-inflammatory, antiviral (17), antidiabetic, antidepressant, anthelmintic, antituberculosis, antimicrobial (18), and antiprotozoal (19), as well as industrial uses in dyes, agricultural chemistry, and medicine. Accordingly, the goal of the current investigation was to create powerful antihyperlipidemic drugs. To assess the effectiveness of compounds, quinoxaline 6a-f has been synthesised, characterised, and tested for its antihyper-lipidemic and antidiabetic properties.

2. Materials and Methods

Materials: All of the compounds were purified using accepted techniques and are of analytical grade. Uncorrected melting points were measured in open capillaries using the Toshniwal equipment. Using a UV lamp as a visualising agent and chloroform: ethyl acetate (7:3) as the solvent system, TLC was utilised to verify the compounds' purity on silica gel G plates. On a Shimadzu 8000 series spectrophotometer, KBr pellets were used to record infrared spectra. Using DMSO-d6 as the solvent and TMS as the internal standard, 1H-NMR spectra were obtained on a Varian EM-200, Avance 200 MHz spectrophotometer (chemical shift values represented in δ ppm). A Shimadzu 2010A series spectrometer was used to record mass spectra using the LC-MS method.

Procedure for the Preparation of 1,4-Dihydroquinoxaline-2,3-dione (1): Diethyl oxalate (0.1 mol) and o-phenylene diamine (0.1 mol) were added to a clean, dry, round-bottom flask, and the mixture was refluxed for one hour. After cooling, the separated solid was filtered, cleaned with 25 millilitres of ether, and then dried. After being recrystallised from DMF, the resulting 2,3-dihydroxy quinoxaline had a melting point of 360 °C and a 90% yield. (20)

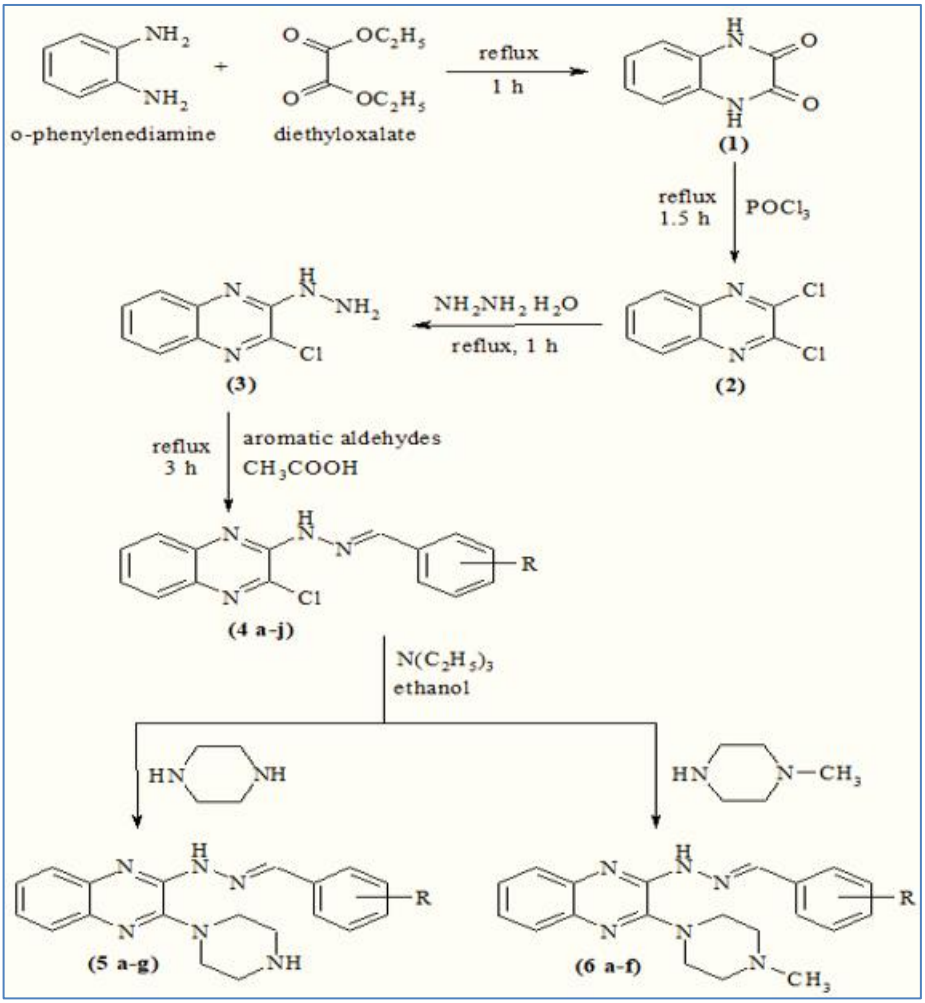
Procedure for the Preparation of 2, 3-dichloro Quinoxaline (2): DMF (1 ml), phosphorous oxychloride (0.04 mol), and 1,4-dihydro quinoxaline-2,3-dione (0.01 mol) (1) were added to a clean, dry, round-bottom flask. Following a 90-minute reflux, the mixture was allowed to cool to ambient temperature before being poured over crushed ice while being continuously stirred with a glass rod. After being filtered, the resulting solid was collected, cleaned with 25 millilitres of water, and allowed to dry. After recrystallising the resulting 2,3-dichloro quinoxaline from a chloroform and n-hexane solution, the yield was 85% and its melting point was 150 °C. (21, 22)

Procedure for the Preparation of 3-chloro-2-Hydrazino Quinoxaline (3): Methanol (25 ml), hydrazine hydrate (0.01 mol), and 2,3-dichloro quinoxaline (0.01 mol) (2) were added to a clean, dry round-bottom flask. For half an hour, the flask's contents were refluxed. Filtration was used to collect the cooled and separated material, which was then cleaned with 25 millilitres of water and dried. After being recrystallised from methanol, the resulting 3-chloro-2-hydrazino quinoxaline has a melting point of 180 °C and a 75% yield. (23)

Preparation of 2-[2-benzylidenehydrazinyl]-3-Chloroquinoxaline (4): 3-chloro-2-hydrazino quinoxaline (0.01 mol) (3), benzaldehyde (0.01 mol), ethanol (25 ml), and glacial acetic acid (1 ml) were added to a clean, dry round-bottom flask. The mixture was refluxed for three hours, cooled, and the separated solid was recovered by filtration, washed with water, and dried. When recrystallised with aqueous ethanol, the resulting 2-[2-benzylidenehydrazinyl]-3-chloroquinoxaline (4a) had a melting point of 247 °C and a 59% yield. A similar process was used to prepare the other Schiff's bases of this series (4b-j). (24) (4g) IR: 3068 cm^{-1} (NH Str), 2931, 2837 cm-1 (Ar-CH Str), 1604 cm-1 (HC=N- Str), 867, 756 cm^{-1} (Disubstituted benzene). 1H NMR: 12.20 δ (1H, s, H of NH-N=), 8.70-8.80 δ (1H, s, CH=N), 6.90- 8.60 δ (8H, m, Ar-H), 3.80-3.90 δ (3H, s, OCH_3). Mass: Molecular weight of the compound is 312 and molecular ion peak was appeared at 311 as M-1. 4i) IR: 3253 cm^{-1} (NH Str), 3068, 3050 cm^{-1} (Ar-CH Str). 1H NMR: 8.15-8.20 δ (1H, s, H of NH-N=), 8.10-8.15 δ (1H, s, H of -N= CH-), 6.90-7.80 δ (8H, m, Ar-H). Mass: Molecular weight of the compound is 300, and the molecular ion peak was appeared at 301 as M+1.

Preparation of 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(piperazin-1yl) quinoxaline (5a): Piperazine (0.01 mol), quinoxaline (4i) (0.01 mol), and 2-chloro-3-[4-(fluorobenzylidene) hydrazinyl] were added to 25 ml of ethanol and 5 ml of triethylamine in a clean, dry round-bottom flask. The mixture was refluxed for 6 hours, cooled, and the separated solid was collected by filtration and dried. When recrystallised with methanol, the resulting 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(piperazin-1yl) quinoxaline (5a) had a melting point of 243°C and a 59% yield. The additional compounds in this series were produced using a similar process, i.e. (5b-g). (25, 26). (5a) IR: 3273 cm-1 (NH Str), 2849 cm-1 (Ar-CH Str), 2723, 2608 cm-1 (CH2 Str). 1H NMR: 10.9 δ (1H, s, 1H of NH), 8.5-8.6 δ (1H, s, 1H of CH=N), 7.0-8.2 δ (8H, m, Ar-H), 4.3-4.4 δ (1H, s, 1H of NH), 3.8-4.0 δ (4H, s, 4H of piperazine), 3.1-3.2 δ (4H, s, 4H of piperazine). Mass: Molecular weight of the compound is 350, and the molecular ion peak appeared at 351 as M+1.

Preparation of 2-[2(3-nitrobenzylidene) hydrazinyl]-3-(4-methyl Piperazin-1-yl) Quinoxaline (6e): 2-chloro-3-[2-(3-nitrobenzylidene) hydrazinyl] quinoxaline (4d) (0.01 mol), N-methyl piperazine (0.01 mol), 25 ml ethanol, and 5 ml triethylamine were added to a clean, dry round-bottom flask. After six hours of refluxing, cooling, and filtration, the separated solid was gathered and allowed to dry. When recrystallised with methanol, the resulting 2-[2-(4-fluorobenzylidene) hydrazinyl]-3-(4-methyl piperazin-1-yl) quinoxaline (6e) had a 50% yield with a melting point of 182 °C. A similar process was used to prepare the additional derivatives of this series (6a-d and f) (27, 28). (6e) IR: 3319 cm^{-1} (NH – Str), 2973, 2850 cm-1 (Ar-CH-Str). 1H NMR: 11.1 δ (1H, s, 1H of NH), 8.8 δ (1H, s, 1H of CH=N), 7.0-8.2 δ (8H, m, 8H of Ar-H), 3.8-4.2 δ (4H, dd, 4H of N-$(CH_2)_2$), 3.3-3.4 δ (2H, d, 2H of N-CH2), 2.1-2.3 δ (2H, d, 2H of N-CH_2), 1.08 δ (3H, s, 3H of CH_3). Mass: Molecular weight of the compound is 391, and the molecular ion peak appeared at 367 as M+1.



Scheme 1: Quinoxaline derivatives

Table 1: Chemical Properties of synthesized compounds(4a-4j)

Deri.	R	Chemical For	M.W	Yield %	M.P.(°C)	Rf Value
4a	H	C15H11N4Cl	283	59	247	0.67
4b	4-OH	$C_{15}H_{11}N_4OCl$	299	49	239	0.63
4c	$N(CH_3)_2$	C17H16N5Cl	326	51	211	0.54
4d	3-NO_2	C15H10N5O2Cl	328	58	237	0.49
4e	2-NO_2	C15H10N5O2Cl	328	45	249	0.38
4f	2-Cl	$C_{15}H_{10}N_4Cl_2$	317	52	259	0.69
4g	4-OCH_3	$C_{16}H_{13}N_4OCl$	312	62	254	0.72
4h	3,4-di OCH_3	C17H15N4O2Cl	343	52	253	0.58
4i	4-F	$C_{15}H_{10}N_4ClF$	300	47	234	0.32

4j	3,4,5-triOCH_3	$C_{18}H_{17}N_4O_3Cl$	373	62	264	0.28

Table 2: Chemical Properties of synthesized compounds(5a-5g)

Deri.	R	Chemical For	M.W	Yield %	M.P.(°C)	Rf Value
5a	4-F	$C_{19}H_{19}N_6F$	340	59	242	0.55
5b	2-Cl	$C_{19}H_{19}N_6Cl$	367	47	143	0.62
5c	4-OH	$C_{19}H_{20}N_6O$	348	52	279	0.44
5d	3,4-di OCH_3	$C_{21}H_{24}N_6O_2$	392	56	216	0.33
5e	4-$N(CH_3)_2$	$C_{21}H_{25}N_7$	375	71	201	0.57
5f	3,4,5-tri OCH_3	$C_{22}H_{26}N_6O_3$	422	75	179	0.59
5g	3-NO_2	$C_{19}H_{19}N_7O_2$	377	67	252	0.47

Table 3: Chemical Properties of synthesized compounds(6a-6f)

Deri.	R	Chemical For	M.W	Yield %	M.P.(°C)	Rf Value
6a	H	$C_{20}H_{22}N_6$	346	42	232	0.51
6b	4-$N(CH_3)_2$	$C_{22}H_{27}N_7$	389	40	252	0.57
6c	3,4,5-tri OCH_3	$C_{23}H_{28}N_6O_3$	436	42	187	0.54
6d	4-F	$C_{20}H_{21}N_6F$	364	44	232	0.49
6e	3-NO_2	$C_{20}H_{21}N_7O_2$	391	50	182	0.48
6f	2-Cl	$C_{20}H_{21}N_6Cl$	381	52	172	0.52

Animals: The Committee for the Purpose of Control and Supervision of studies on Animals (CPCSEA) criteria were followed in conducting the studies. For the experiment, adult Swiss albino mice of either sex weighing between 20 and 30 g will be chosen. Every animal will have a 12-hour light-dark cycle, be kept at room temperature (22 ± 1 °C), and have a relative humidity of 55 ± 1%. The animals will have unrestricted access to water and a typical pellet diet. (29, 30)

Antihyperlipidemic and Antidiabetic Activity: Mice were given a high-fat diet, with the exception of the normal control group, in order to cause diabetes. A single intraperitoneal injection of streptozotocin (35 mg/kg; STZ in citrate buffer, pH 4) will be given at the conclusion of the second week of dietary manipulation, and the high-fat diet feeding will continue. Following the increase in blood glucose, a synthetic substance was administered at a dose of 10 mg/kg of body weight to begin treatment. Up to five weeks, general factors such as body weight, food intake, and water intake were tracked on a regular basis. Each animal's tail vein was used to draw blood, and the serum was separated and used to measure total cholesterol, LDL, HDL, triglycerides, and glucose. (31, 32)

Statistical Analysis: Individual mice were used as an experimental unit to measure changes in the levels of glucose, triglycerides, LDL, HDL, and total cholesterol. Standard deviations and mean values were used to express each outcome. The one-way ANOVA approach was used to analyse the data. (33, 34)

3. Results and Discussion

Antidiabetic and Antihyperlipidemic Activity: Adult Swiss albino mice were used to screen all of the synthesised compounds for antidiabetic and antihyperlipidemic properties. The produced compounds have antihyperlipidemic and antidiabetic properties. All of the treatment groups' serum levels of glucose, triglycerides, LDL, HDL, and total cholesterol were assessed; the findings are displayed in Table 4. Streptozotocin (disease control) significantly raised the levels of glucose, triglycerides, LDL, and total cholesterol when compared to the normal control. When compared to the normal control, streptozotocin significantly reduced the HDL levels in the diabetic and hyperlipidemic control groups.

Effect of Synthesized Compounds (6a-6f) on Serum Level of Glucose, Triglyceride, LDL, HDL and Total Cholesterol: When mice are given synthetic quinoxaline derivatives (compounds 6a and 6d) orally, their serum levels of glucose, triglycerides, LDL, and total cholesterol are much lower than those of the disease control. Compared to the illness control, mice treated with compounds 6a and 6d showed a considerable rise in their serum HDL levels. Table 4 displayed the outcomes.

Table 4: Effect of Different Derivatives of quinoxaline on Serum Glucose, Triglyceride, LDL, HDL and Total Cholesterol Level in Diabetic Mice

Groups	Treatment Dose (mg/kg)	Glucose (mg/dl)	TG (mg/dL)	LDL (mg/dl)	HDL (mg/dl)	TC (mg/dl)
Comp 6a	10	165.41±3.11*	57.45±1.42	47.99±3.63*	42.32± 2.46*	240.15±3.95*
Comp 6b	10	278.13±1.67	105.16±2.45	104.21±3.17	34.36± 3.73	365.47±5.77
Comp 6c	10	219.45±2.31	137.84±3.51	98.76± 2.53	35.77±3.11	345.11±4.84
Comp 6d	10	185.49±3.28*	81.63±2.17*	69.56± 3.52*	43.51±1.43*	287.56±5.42*
Comp 6e	10	203.65±2.11	92.17±3.63	88.65±1.57	31.76±2.65	309.97±5.23
Comp 6f	10	197.45±4.11	89.11±2.67*	73.37±2.05*	37.11± 2.14	297.55±3.63
Normal Control	Vehicle	84.56±1.79	85.11±3.11	34.54±2.53	50.11±3.56	95.11± 3.56
Disease Control	150	302.11±1.85	141.36±4.83	108.45±2.42	33.28± 2.87	376.45±5.76
Std Drug	3	145.56±2.11	42.96±1.56	35.11±2.31	46.27± 2.43	221.27±4.68

Results are expressed in mean ± SEM (n=6), STZ = streptozotocin, TG = triglyceride, LDL = low density lipoprotein, HDL = high density lipoprotein, TC = total cholesterol. The data were analyzed by one-way ANOVA followed by Dunnett test, and difference *P<0.05 were considered statistically significant as compared with Vildagliptin 3 mg/kg.

The current study examines quinoxaline derivatives' antidiabetic and antihyperlipidemic effects in mice with STZ-induced diabetes. It is commonly acknowledged that STZ can cause diabetes in rodent models, and that the resulting diabetes is similar to diabetes mellitus in humans. In order to assess the antidiabetic effects of different substances, vildagliptin is frequently employed as a standard antidiabetic medication in STZ-induced diabetes. According to the current study, giving mice quinoxaline derivatives (Compounds 6a and 6d) at a dose of 10 mg/kg considerably lowers their serum glucose levels when they have STZ-

induced hyperglycemia. The unchecked action of lipolytic hormones on fat depots and the increased mobilisation of fatty acids from fatty tissues may be the cause of the marked hyperlipidaemia that occurs in diabetes. Increased levels of glucose, triglycerides, low-density lipoproteins, and total cholesterol, as well as lower levels of high-density lipoproteins, are linked to diabetic hyperlipidaemia. Patients with diabetes mellitus are more likely to develop coronary heart disease as a result of these alterations. The risk of cardiovascular illnesses is closely correlated with a rise in LDL and a fall in HDL. The current study demonstrates that administering quinoxaline derivatives (Compound 6a and 6d) to patients with STZ-induced diabetes lowers lipid markers like TG, TC, and LDL and raises HDL cholesterol levels. Because HDL cholesterol aids in the removal of excess cholesterol from the body, it is essential in the prevention of cardiovascular illnesses.

4. Conclusion

In the current study, quinoxaline derivatives were synthesised, and the structures of the compounds were determined by IR, 1HNMR, and mass spectroscopy. The TSZ-induced diabetes model was used to screen the compounds for antidiabetic and antihyperlipidemic properties. Perhaps molecules with enhanced activity will result from the molecular change. In summary, the current research showed that the recently synthesised quinoxaline derivatives have notable antihyperlipidemic and antidiabetic effects on mice with STZ-induced diabetes. Additional research to determine the mechanism of these substances may be useful for future clinical investigations.

References

1. Vishvakrama P, Sharma S. Liposomes: an overview. Journal of Drug Delivery and Therapeutics. 2014 Jun 24:47-55.
2. Vishvakarma P. Design and development of montelukast sodium fast dissolving films for better therapeutic efficacy. Journal of the Chilean Chemical Society. 2018 Jun;63(2):3988-93.
3. Vishvakarma P, Mandal S, Verma A. A review on current aspects of nutraceuticals and dietary supplements. International Journal of Pharma Professional's Research (IJPPR). 2023;14(1):78-91.
4. Prabhakar V, Agarwal S, Chauhan R, Sharma S. Fast dissolving tablets: an overview. International Journal of Pharmaceutical Sciences: Review and Research. 2012;16(1):17.
5. Mandal S, Vishvakarma P, Verma M, Alam MS, Agrawal A, Mishra A. Solanum Nigrum Linn: an analysis of the Medicinal properties of the plant. Journal of Pharmaceutical Negative Results. 2023 Jan 1:1595-600
6. Yue EW, Wayland B, Douty B, Crawley ML, McLaughlin E, Takvorian A, Wasserman Z, Bower MJ, Wei M, Li YL, Ala PJ, Gonneville L, Wynn R, Burn TC, Liu PCC, Combs AP. Isothiazolidinone heterocycles as inhibitors of protein phosphatases: synthesis and structure-activity relationships of a peptidescaffold. Bioorg. Med. Chem. 2006;14:5833–5849. doi: 10.1016/j.bmc.2006.05.032. [DOI] [PubMed] [Google Scholar]
7. Moreno-Diaz H, Villalobos-Molina R, Ortiz-Andrade R, Diaz-Coutino D, Medina-Franco J L, Webster SP, Binnie M, Estrada-Soto S, Ibarra-Barajas M, Leon-Rivera I, Navarrete-Vazquez G. Antidiabetic activity of N-(6-substituted-1,3-benzothiazol-2-yl)benzenesulfonamides. Bioorg. Bioorg. Med. Chem. Lett. 2008;18:2871–2877. doi: 10.1016/j.bmcl.2008.03.086. [DOI] [PubMed] [Google Scholar]
8. Du Z-Y, Liu R-R, Shao W-Y, Mao XP, Ma L, Gu L-Q, Huangm Z-S, Chan ASC. Alpha-glucosidase inhibition of natural curcuminoids and curcumin analogs. Eur J Med Chem. 2006; 41: 213-18.
9. Eaton PE and Carlson GR. Phosphorous pentoxide-methanesulfonic acid. Convenient alternative to polyphosphoric acid. J Org Chem. 1973; 38: 4071-73.
10. Galt RH, Horbury J, Matusiak ZS, Pearce RJ, Shaw JS. Thexanthene-9-spiro-4'-piperidine nucleus as a

probe for opiate activity. J Med Chem. 1989; 32: 2357-62.
11. Heightman, TD, Andrea T, Vasella AT. Recent insights into inhibition, structure, and mechanism of configuration-retaining glycosidases. Angew Chem Int Ed. 1999; 38: 750-70.
12. Humphries MJ, Matsumoto K, White SL, Olden K. Inhibition of experimental metastasis by castanospermine in mice: Blockage of two distinct stages of tumor colonization by oligosaccharide processing inhibitors. Cancer Res. 1986; 46: 5215-22.
13. Karpas A, Fleet GW, Dwek RA, Petursson S, Namgoong SK, Ramsden NG, Jacob GS, Rademacher TW. Aminosugar derivatives as potential anti-human immunodeficiency virus agents. Proc Natl Acad Sci USA. 1988; 85: 9229-33.
14. Sajjadifar S., Nezhad E.R. Qinoxaline III. synthesis of quinoxaline derivatives over highly efficient and reusable bronsted acidic ionic liquids. Int. J. ChemTech Res. 2013;5:2041–2050. [Google Scholar].
15. Aravind K., Ganesh A., Ashok D. Microwave assisted synthesis, characterization and antibacterial activity of quinoxaline derivatives. J. Chem. Pharm. Res. 2013;5:48–52. [Google Scholar].
16. Liu Y, Zou L, Ma L, Chen W-H, Wang B, Xu ZL. Synthesis and pharmacological activities of xanthone derivatives as a-glucosidase inhibitors. Bioorg Med Chem. 2006; 14: 5683–90.
17. Ali M.M., Ismail M.M.F., El-Gaby M.S., Ammar Y.A. Synthesis and antimicrobial activities of some novel quinoxalinone derivatives. Molecules. 2000;5:864–873. doi: 10.3390/50600864. [DOI] [Google Scholar]
18. Wadavrao S.B., Ghogare R.S., Narsaiah A.V. A simple and efficient protocol for the synthesis of quinoxalines catalyzed by pyridine. Org. Commun. 2013;6:23–30. [Google Scholar]
19. Ismail M.M.F., Nofal S.M., Ibrahim M.K., El-Zahaby H.S.A., Ammar Y.A. 3-Ethoxy-carbonylmethylenequinoxaline-2-one in heterocyclic synthesis (part 2): Synthesis and pharmacological evaluation of new 6,7-dimethyl quinoxalines as potential nonulcerogenic, anti-inflamatory and analgesic agents. Afinidad. 2006;63:689–696. [Google Scholar]
20. Ismail M.M.F., Ammar Y.A, Ibrahim M.K., El-Zahaby H.S.A. Synthesis and pharmacological evaluation of novel quinoxalines as potential nonulcerogenic, anti-inflammatory and analgesic agents. Arzneimittelforschung. 2004;55:738–743. doi: 10.1055/s-0031-1296923. [DOI] [PubMed] [Google Scholar]
21. Rodrigues F.A.R., Bomfima I.D.S., Cavalcanti B.C., Pessoa C.D.Ó., Wardell J.L., Wardell S.M., Pinheiro A.C., Kaiser C.R., Nogueira T.C.M., Low J.N., et al. Design, synthesis and biological evaluation of (E)-2-(2-arylhydrazinyl)quinoxalines, a promising and potent new class of anticancer agents. Bioorg. Med. Chem. Lett. 2014;24:934–939. doi: 10.1016/j.bmcl.2013.12.074. [DOI] [PubMed] [Google Scholar]
22. Ismail M.M.F., Amin K.M., Noaman E., Soliman D.H., Ammar Y.A. New quinoxaline-1,4-di-N-oxides: Anticancer and hypoxia-selective therapeutic agents. Eur. J. Med. Chem. 2010;45:2733–2738. doi: 10.1016/j.ejmech.2010.02.052. [DOI] [PubMed] [Google Scholar]
23. Amin K.M., Ismail M.M.F., Noaman E., Soliman D.H., Ammar Y.A. New quinoxaline-1,4-di-N-oxides (part 1): Hypoxia-selective cytotoxine and anticancer agents derived from quinoxaline-1,4-di-N-oxides. Bioorg. Med. Chem. 2006;14:6917–6923. doi: 10.1016/j.bmc.2006.06.038. [DOI] [PubMed] [Google Scholar]
24. Farrag A.A., Ammar Y.A., El-Sehemi A.G., Thabet H.Kh., Hassan N.A., Samy A.Kh. Synthesis and pharmacological screening of novel sulfamoylphenyl carbamoylquinoxaline derivatives as anti-inflammatory, analgesic and antitumour agets. J. Chem. Res. 2011;163:163–166. doi: 10.3184/174751911X12983997221326. [DOI] [Google Scholar]
25. Suresh M., Lavanya P., Sudhakar D., Vasu K., Rao C.V. Synthesis and biological activity of 8-chloro-[1,2,4]triazolo[4,3-a]quinoxalines. J. Chem. Pharm. Res. 2010;2:497–504. [Google Scholar]
26. Noolvi M.N., Patel H.M., Bhardwaj V., Chauhan A. Synthesis and in vitro antitumor activity of substituted quinazoline and quinoxaline derivatives: Search for anticancer agent. Eur. J. Med. Chem. 2011;46:2327–2346. doi: 10.1016/j.ejmech.2011.03.015. [DOI] [PubMed] [Google Scholar]