

## Chemistry and pharmacological diversity of quinoxaline motifs as anticancer agents

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Surpassing heart diseases, cancer is taking the lead as the deadliest disease because of its fast rate of spreading in all parts of the world. Tireless commitment to searching for novel therapeutic medicines is a worthwhile adventure in synthetic chemistry because of the drug resistance predicament and regular outbreak of new diseases due to abnormal cell growth and proliferation. Medicinal chemistry researchers and pharmacists have unveiled quinoxaline templates as precursors of importance and valuable intermediates in drug discovery because they have been established to possess diverse pharmacological potentials. Hence, this review highlights the current versatile routes to accessing functionalized quinoxaline motifs and harnessing their documented therapeutic potentials for anticancer drug development.

*Keywords:* quinoxaline, anticancer activity, pharmacophore

### INTRODUCTION

Cancer is a predicament that has received considerable attention as a top-rated killer disease, which is responsible for over 70 % cases of mortality in less developed countries. Based on the consistent rise in the statistical data on cancer related deaths, it has been forecast that 11.5 million deaths will be recorded by the year 2030 (1). Cancers mainly occur as a result of mutagenicity in the gene encoding DNA. This results in the abnormal cell trait leading to rapid spread of abnormal cells that destroy neighboring tissues and could quickly spread to other parts of the body (2). Outbreak of tumor-related multidrug resistance (MDR) is a crucial reason for the widely reported failure rate in cancer therapy. The incidence of resistance among commercially available anticancer drugs has created more avenues for further quest for newer molecular entities for the therapeutic fight against cancer (3). The extra mass of tissues formed when cells are proliferating abnormally where they are not required are called tumors. They may be either benign or malignant, and the latter are cancerous and require disease control and prevention (4). According to molecular mechanisms, imidazolquinoxalines have been reported to show strong anticancer potential, which resulted from TNF- $\alpha$  production impairment through activation of p38MAPK

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pathway and inhibition of PI3K pathway in the L929 murine fibroblast cell line (5). Thymidine kinase 1 (TK1) and thymidine phosphorylase (TYMP) are key molecular targets of thymidine therapeutics in cancer treatment. Hence, cytosolic thymidine pathways have been documented to be a highly effective tool in the modulation of anticancer activity of a thymidine quinoxaline conjugate (6). In view of the adverse effect of this global phenomenon, various researchers have synthesized numerous nitrogen containing heterocyclic compounds as agents of transformation in anticancer motifs in the chemotherapeutic world. For instance, some commercially available anticancer heterocycles include benzimidazole-based nocodazole (7), quinazoline-based KYS05090 (8), pyrimidine-based 5-fluorouracil and quinoline-based camptothecin (9).

Over the years, heterocycles have been the largest areas of research in organic chemistry. Numerous biologically relevant compounds such as most of the phytochemicals and secondary metabolites as well as nucleotides contain heterocyclic rings. Quinoxaline falls into the class of benzodiazines and it has its heteroatomic nitrogen located at positions 1- and 4- of the heterocyclic nucleus (10). Latest information has unveiled quinoxaline nucleus as a privileged template among nitrogen-based heterocycles owing to its numerous valuable chemical properties (11), utilization in materials science research (12) and diverse pharmacological potentials (13). Hence, it is worthwhile targeting a review at quinoxaline as a dynamic heterocyclic compound to open more windows of opportunities among anticancer drugs.

#### PHYSICAL PROPERTIES OF QUINOXALINE

Quinoxaline (also 1,4-benzodiazine, 1,4-diazinaphthalene, 1,4-naphthyridine, benzo-paradiazine,  $C_8H_6N_2$ ,  $M_r$  130.15) is a low melting solid. It melts at 29–32 °C just above room temperature. Its boiling point is 220–223 °C. It is weakly basic ( $pK_a$  0.60). It is miscible with water and has a density of 1.124 g mL<sup>-1</sup> at 25 °C (14). Quinoxaline frameworks are frequently reported to be from synthetic sources. Incorporation of at least one phenyl moiety in quinoxaline, as well as a structurally related heterocycle such as phenazine, increases the total number of resonance hybrids for such quinoxaline derivatives (4).

#### OVERVIEW OF CANCER

Cancer could be described as a compounded disorder that could be traceable elementarily to an environmental phenomenon. Carcinogens have been reported to be encountered by people through their exposure to water, air, chemicals, sunlight and food (15). It is interesting to note that more than 90 % of cancers happen in the epithelia since epithelial cells cover a significant part of the body such as skin, respiratory and alimentary tracts. They also play a crucial role in metabolizing the ingested carcinogens (16). Mutations of the protein-encoding genes which control cell division are often responsible for the discrepancy and anomalies in cancer cells. This is because the proteins that are responsible for repairing worn-out cells and DNA damage are made by malfunctioning genes, which genes are also mutated. Treatment of cancer cells with DNA2 inhibitors recapitulates phenotypes observed upon DNA2 depletion, including reduced DNA double-strand break end resection and attenuation of HR repair. Similarly to genetic ablation of DNA2, chemical inhibition of DNA2 selectively attenuates the growth of various cancer cells with oncogene-induced replication stress (17).

Inconsistent with the highly regulated physiological processes in normal cells, cancer cells undergo autonomous metabolic reprogramming to maintain rapid growth and proliferation and escape from growth suppressors and cell death signaling. Numerous cell signaling pathways are implicated in the induction and maintenance of epithelial mesenchymal transition (EMT), such as TGF- $\beta$ , Wnt/ $\beta$ -catenin, Notch and oncogenic Src or Ras signaling (18), and the zinc finger E-box binding homeobox (ZEB) family transcriptional factors involved in the EMT processes are ZEB1 and ZEB2. Cancer is recognized by the uninhibited development of cells without differentiation caused by the de-regulation of proteins controlling cell division, cell multiplication and, also some critical enzymes (17). Recently, low protein diets have been reported to be associated with lowered cancer incidence and mortality risk of cancers in humans. In murine models, protein restriction inhibits tumor growth *via* the mTOR signaling pathway. IGF-1, amino acid metabolic programming, FGF21, and autophagy may also serve as potential mechanisms of protein restriction mediated cancer prevention (19). The dietary intervention aimed at reducing protein intake can be beneficial and has the potential to be widely adopted and effective in preventing and treating cancers (19). The beneficial role of low protein diets in tumor growth and cancer outcomes has been observed in numerous studies. For example, the result of a study showed a 70 % inhibition of tumor growth in the castrate-resistant Lu-CaP23.1 prostate cancer model and a 56 % inhibition in the WHIM16 breast cancer model fed a 7 % protein diet when compared to an isocaloric 21 % protein diet (20).

### *Causes of cancer*

There are diverse causes of cancer which are noted to be complicated in nature, comprising factors in the ecosystem and cells. Considerable attention has been directed towards unveiling the major causes of cancer, some of which are herein underlined as tobacco smoke carcinogens, alcohol consumption, dietary factors, body mass and obesity, physical inactivity and inherited genetic abnormality.

*Tobacco smoke carcinogens.* – Statistical estimation has shown that cigarette consumption is accountable for the annual mortality rate of over one million human beings *via* lung cancer and diverse other neoplasms. Mutation loads are usually greater with an excess of G to T transversions among cancers traceable to smoking, which in turn results in higher frequency of p53 mutations (2). According to a recent study, the risk of conditional breast cancer specific death rate was on the increase amidst female population with recurring smoking habits compared to women that never smoke (21, 22).

*Alcohol consumption.* – It has been asserted that alcohol consumption plays a crucial role in the recent drastic increase in cancer cases (23, 24). According to the summary of a review, heavy alcohol consumption (more than four bottles per day) was significantly related to elevated risk of cancer associated with mouth and alimentary canals (24). Although the biological mechanism is not yet fully understood, the report on an epidemiological study supports the verdict which says high alcoholic consumption causes cancerous cells manifestation in seven crucial parts of the human body (25). A study on drinking and health risk clearly showed that the risk of death from liver diseases caused by alcohol consumption skyrocketed (Fig. 1) after consumption of a couple of drinks per day (26).

*Dietary factors.* – People's daily feeding habits have a direct impact on either averting or conferring risks. Improvement of daily fruit and vegetables intake cannot be overem-

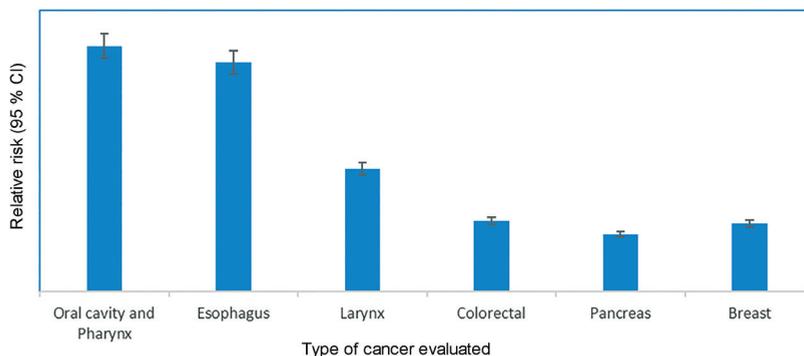


Fig. 1. Heavy alcohol consumption and the risk of selected cancers. Estimates for alcohol consumption of 4 or more drinks per day *vs.* non/occasional drinkers, except for pancreatic (*i.e.*,  $\geq 3$  drinks per day *vs.* non/occasional drinkers) and breast (*i.e.*,  $\geq 4.5$  drinks per day *vs.* non-drinkers) cancers; SD bars,  $n = 3$  (drawn based on raw data from ref. 24). CI – confidence interval.

phased in the promotion of a healthy diet in order to prevent and avert insurgence of abnormal cell proliferation, chronic diseases and various disorders (27). Total cholesterol, triglyceride levels and glycaemic load should be monitored and controlled in breast cancer risk populations because they may be associated with increased risk. High intake of polyphenol/phyto-oestrogen-rich food (*i.e.*, flavonoids, soya products), as well as fibers, fruits and vegetables, may have potential protective effects against breast cancer occurrence but the results might vary according to hormonal status (28).

Evidence of the relationship between dietary habits and cardiovascular disorder risks among the middle-aged population and elderly persons has been reported in literature (28). Factors contributing to the reduction of cardiovascular disease and cancer incidence would contribute tremendously to improvements in health and longevity (29).

*Body mass and obesity.* – Body mass and obesity provide estimated statistics of roughly twenty percent of documented cancerous cell issues (30). Excess body mass might have a direct or indirect effect on cancer risk in some ways. Surplus body fat may have a direct impact on the immune system dependent factors, inflammation and the amount of some hormones such as insulin and estrogen. It can also affect factors that control cell growth and hormonal regulatory proteins that regulate effective utilization of such hormones by the body system (31). Weight gain in already diagnosed breast cancer patients was reported to increase the risk, while weight loss might reduce the risk (32).

*Physical inactivity.* – Improvement in the quality of life of subjects after the diagnosis of breast cancer (33) and bladder cancer (34) was documented to be directly related to physical activity (35). Life survival among the physically active mature female population diagnosed with breast cancer could be efficiently improved by lower estrogen levels in such subjects; though there are insufficient data to support this hypothesis (36).

*Inherited genetic abnormality.* – There have been cases showing that genetic abnormality inherited by the subjects could be an underlying factor in many cancer cases. Most cancerous cells result from genetic structural changes due to a lack of control mechanisms responsible for the prevention of cancerous cell development (37). The gene encoding portion of

cancer was found to have the ability to cluster in families (38, 39). Cancers are considered to be hereditary in nature and are related to the sudden change in the appearance of inherited genes. Inherited breast cancers are known to occur earlier in life compared to sporadic types which are known to be non-inherited (40). Abnormalities in the cell cycle progression are caused by a disruption that resulted from the loss of functioning ability of tumor suppressor genes. Cancer is the crucial disease that the geneticists have been fighting against and is found to be hard to unveil at the molecular level. It is known to exist continuously in families (41).

### Demographic data

Information about the incidence of some common cancers across various regions of the world has been reported (42) and the results are shown in Table I.

Table I. Estimated age-standardized incidence and mortality rates per 100,000 subjects in different world areas

Continent	Region	Incidence		Mortality	
		Male	Female	Male	Female
Africa	Eastern Africa	121.2	125.3	105.4	95.9
	Central Africa	88.1	96.7	78.5	75.6
	Northern Africa	109.2	98.9	89.5	68.2
	Southern Africa	235.9	161.0	172.1	108.1
	Western Africa	92.0	123.5	80.1	91.2
Asia	Eastern Asia	222.1	158.1	155.5	87.3
	South-Central Asia	99.7	110.8	78.0	71.7
	South-Eastern Asia	143.9	141.7	112.3	89.4
	Western Asia	152.8	119.5	113.9	74.3
North America	Caribbean	196.3	153.5	116.6	86.2
	Central America	136.2	134.4	84.7	80.6
	North America	334.0	274.4	122.4	91.5
South America	South America	186.7	162.9	116.6	88.2
Europe	Central and Eastern Europe	259.2	184.2	181.5	94.0
	Northern Europe	292.3	249.5	134.6	99.7
	Southern Europe	289.9	212.2	149.9	81.2
	Western Europe	337.4	250.9	138.4	84.3
Australia	Australia/New Zealand	356.8	276.4	125.6	86.0
	Melanesia	146.0	133.4	119.8	95.9
	Micronesia	153.8	164.4	104.7	70.3
	Polynesia	225.0	201.5	133.6	87.9

<sup>a</sup> Source: ref. 37.

Overall cancer incidence and mortality rates by sex across the world are shown in Table I. The sample population used per region is 100,000. The incidence rate for both sexes combined is more than 3 times as high in Australia/New Zealand (633.2) as that in central Africa (184.8). It was noticed that the incidence was consistently higher in male than in female subjects in all regions of Asia, Europe and the Caribbean, except for South-Central Asia where the incidence in females was higher than that in males by 11 % (Table I). There is less regional variability in mortality than in incidence. Male mortality rate is higher than that of females in all African sub-regions except in Western Africa where the reverse was the case. Overall, the highest mortality rate for men was found in Central and Eastern Europe while that of women was highest in Southern Africa (42). Cancer cases have been decreasing in several western countries, largely owing to improved treatment and increased awareness and early detection; rates continue to increase in many countries with more limited resources and health infrastructure, particularly in Central and South America and Eastern Europe.

Breast cancer in females and lung cancer in males are the most frequently diagnosed cancers and the leading cause of cancer death for each sex in both economically developed and developing countries, while lung cancer is preceded by prostate cancer as the most frequent cancer among males in economically developed countries (42).

### *Types of cancer*

Cancer has been categorized using various parameters of paramount importance. Some of the main types of cancer have been estimated based on the number of deaths. The most common types discussed in this study include lung cancer, leukemia, colorectal cancer, liver cancer and breast cancer.

*Lung cancer.* – Lung cancer has been also referred to as pulmonary carcinoma. The highest factor that often results in lung cancer is smoking (43). It has been reported that the second hand smoking of radon and particulate matters related to air pollution agents such as benzene (44), formaldehyde (44) and diesel air pollutants (45) are other identified sources of lung cancer. The symptoms include consistent coughing, concise and interrupted breath, puffing sound, bloody spittle, continuous bronchitis and other chest pain related issues (46). Subjects with small cell lung cancer (SCLC) were reported to have stronger initial response to chemotherapy than those with non-small cell lung cancer (NSCLC) (47, 48) although they are both responsible for eighty-five percent of lung cancer (47).

*Leukemia.* – Leukemia originates from cells that are essential to new blood cell formation (49). Cells of these types are found in the bone marrow. Leukemia, having started in the soft inner parts of the bone, is then transported to other parts of the body through the blood stream (50). There are indications that any cell responsible for blood formation could change to leukemia. They can develop into one of the three main types of blood cells (51). Acute lymphocytic leukemia (ALL), also called acute lymphoblastic leukemia, progresses rapidly and if not treated could be fatal according to the findings of an earlier review (52). Some of the major causative agents of leukemia are the degree of exposure to radiation (53), exposure to hazardous chemicals (54), viral infections (55), certain inherited syndromes. Treatments for leukemia include chemotherapy, radiation therapy, targeted therapy, stem cell transplant (56).

*Colorectal cancer.* – Colorectal cancer can be described as a type of cancer that originates from either the colon or the rectum (57, 58). It was unveiled by epidemiological studies

as the third most virulent class of cancer globally (59). Most colorectal cancers develop gradually over many years. Prior to the commencement of cancer development, a non-cancerous polyp on the inner wall of either colon or rectum often initiates tissue or tumor growth (60). There are certain risks that can cause this type of cancer. These include: the type of diet (eating meat cooked at high temperature might cause statistical odds of getting colorectal cancer), lack of physical exercise, obesity, smoking, high alcohol consumption, individual record of stomach inflammatory disease, genealogical record of colorectal cancer events, inherited syndromes (61) among others. Colorectal cancer has symptoms such as excessive blood loss through the rectum, mental exhaustion, weariness, fatigue, unwanted weight loss, hematochezia, cramps and abdominal pain (62). Prevention of colorectal cancer, primary or secondary (63), could involve screening of the population without symptoms of cancer or pre-cancer conditions (64).

*Liver cancer.* – Liver cancer incidence is more rampant in developing countries (65). Cases of HBV and HCV were reported to be a crucial risk factor for liver cancer, also known as hepatocellular carcinoma (66). Among the human population in developing countries, intake of contaminated food items possessing mycotoxins, aflatoxin, along with active hepatitis virus infection constitutes a salient risk (67). In addition to these, excessive alcohol intake is also among odds for liver cancer in industrialized nations of the world through the development of cirrhosis and alcoholic hepatitis (68). The early stage of liver cancer can be treated by surgery; however, the removal of affected tissues *via* radiofrequency, chemo-embolization or alcohol insertion could be alternative treatments to surgery (1).

*Breast cancer.* – Breast cancer is a form of tumor with malignant traits that originates in breast cells (69). One of the ways in which breast cancer can spread is *via* the lymph system, which is a salient point to comprehend breast cancer (70). Most breast cancers are cancers that originate from the epithelial cells which shape breast tissues and are referred to as carcinomas (71). This cancer can also be transferred genetically. Women who started menstruating early have a higher chance of this menace, probably due to the long lasting period of exposure to progesterone and estrogen (71). Other risk factors are alcohol consumption, physical inactivity. There are some steps that can be undertaken to reduce the risk.

## MALIGNANT TUMORS

Formation and development of malignant tumors can start in cellular parts of any organ with a high tendency of involvement in replication. Tumors of epithelial tissue include sarcoma of soft tissues and bone, glioma (brain), leukemia and lymphoma (hematopoietic and lymphatic tissues). Carcinomas are the most frequent class (72). Cancer cells have the tendency to produce two types of tumors, either the non-cancerous (benign tumors) or cancerous type (malignant tumors). Malignant tumors, generally categorized as carcinomas and sarcomas (73), can grow rapidly and harmfully, thereby destroying parts of tissues and organs in proximity to the tumor site (74).

Progression of malignancy begins with mutation and proceeds through hyperplasia, dysplasia to *in situ* cancer and/or invasive cancer (75). A typical malignant tumor is malignant mesothelioma; some of its symptoms are painful abdomen, inflammation or accumulation of fluid in the abdomen, weight loss, nausea, vomiting and constipation. Reports

have also shown that these malignant mesotheliomas are more common in men than women (76). The best way malignant mesothelioma can be prevented is by limiting the exposure to asbestos at home, workplace or even public places (77). These tumors can be diagnosed early using various spectroscopic techniques (78).

#### QUINOXALINE – PRIVILEGED HETEROCYCLE

Owing to the privileged nature of functionalized quinoxaline heterocycle, quinoxaline-carbohydrate hybrids have been designed and evaluated as new and selective agents of impact in cytotoxic activity and photochemically induced cleaving in DNA (79). Quinoxaline-based compound **1**, coded as XK469, belongs to the class of quinoxalines with anti-tumor efficiency and is structurally related to compound **2**, commonly called chloroquinoxaline sulfonamide, CQS (NSC-339004). Quinoxaline-based compounds **1** and **2** are both known as antineoplastic quinoxaline topoisomerase II inhibitors (80). Quinoxaline 1,4-di-N-oxides (QdNOs) have manifold biological properties. Recent development of QdNOs, **3**, **4** and **5**, which are non-toxic until they are activated in the hypoxic cell, opens a new era in anticancer drug discovery (81). Numerous quinoxaline frameworks are currently under preclinical as well as clinical trial studies to be considered in effective treatment of infectious diseases. Quinoxaline compound **6**, coded as BMS345541, is a kinase inhibitor which is utilized as an anti-tumor agent (82), while quinoxaline **7**, coded as NVP-BSK805, is being developed as a valuable candidate for treating tumors and polycythemia (83) (Fig. 2).

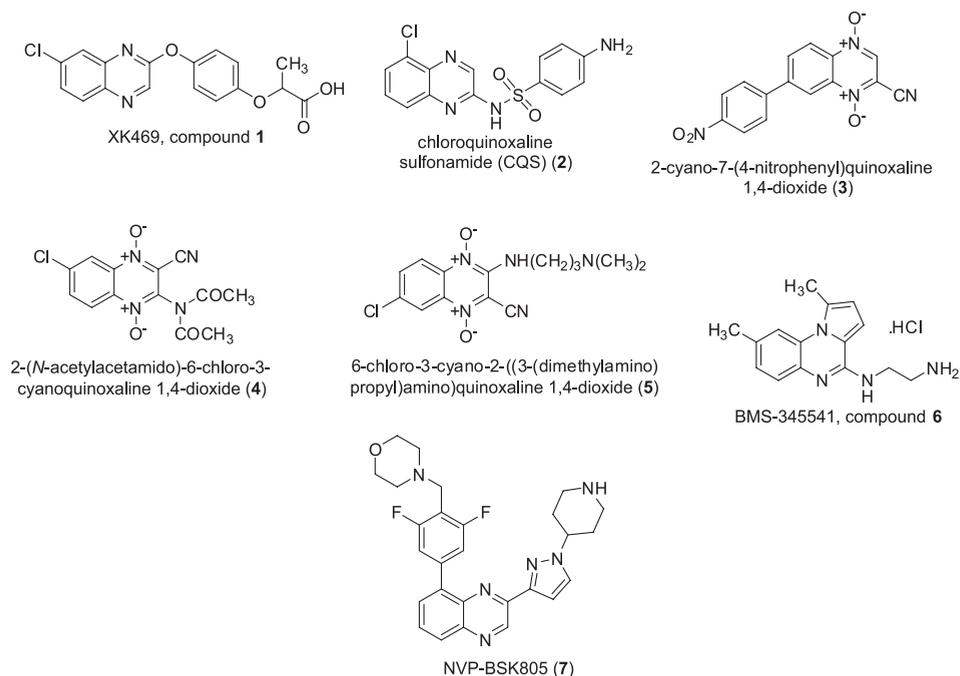


Fig. 2. Some quinoxaline-based drugs and drug-like candidates as anticancer agents (ref. 83).

## NATURAL OCCURRENCE OF QUINOXALINES

Quinoxaline is the valuable core structure found in echinomycin (**8**), which is a naturally occurring polypeptide antineoplastic antibiotic isolated from the bacterium *Streptomyces echinatus*. Echinomycin is known to be a strong inhibitor of RNA synthesis, which is attributed to its ability to bind to double-helical DNA. Echinomycin has also been isolated from *Streptomyces lasaliensis*. It belongs to the family of quinoxaline antibiotics (84). There are interesting facts ascribable to this series of compounds due to the effective and efficient anticancer and antimicrobial activities they possess. Echinomycin biosynthesis, with the structure, as shown in Fig. 3, started with a molecule of quinoxaline-2-carboxylic acid (QC).

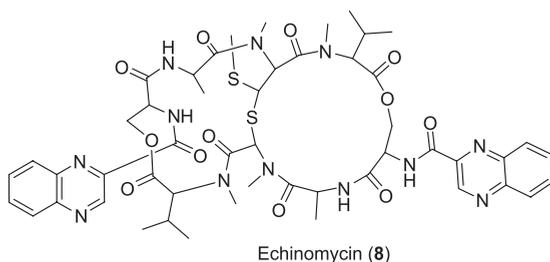


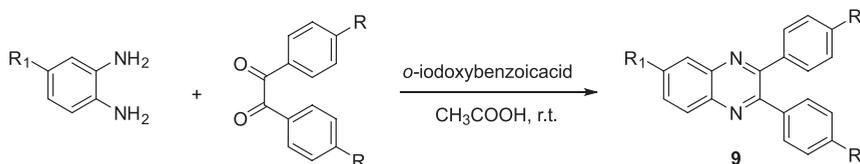
Fig. 3. Naturally occurring quinoxaline-based antibiotic and anticancer agent echinomycin (**8**).

L-tryptophan is the precursor of quinoxaline-2-carboxylic acid (QC) and its biosynthesis paralleled the first stage of nikkomycin biosynthesis (84). Quinoxaline is a benzopyrazine and this pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro form in luciferin of several beetles including the firefly responsible for the chemiluminescence of this ostracod. Methoxypyrazine is a very important component of the aroma of many fruits and vegetables such as peas and *Capsicum* peppers, and also of wines (85).

#### Synthesis of quinoxaline and its derivatives

(i) Condensation reaction of *p*-substituted benzyl with *o*-phenylene diamines was reported to proceed readily and effectively using *o*-iodoxybenzoic acid (IBX) as catalyst at 25 °C to furnish 2,3,6-trisubstituted quinoxaline derivative (**9**), as shown in Scheme 1 (86).

(ii) According to the previous findings from our laboratory, hydrazinolysis of quinoxaline-2,3-dione gave 3-hydrazinoquinoxalin-2(1*H*)-one (**10**), which subsequently underwent microwave-assisted reaction with indole-2,3-dione derivatives (isatin derivatives) to furnish

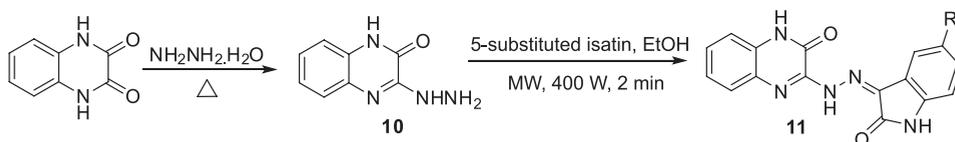


Scheme 1

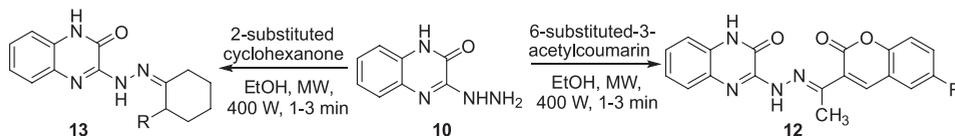
the corresponding quinoxalinone hydrazones, 3-(2-(5-substituted-2-oxindolin-3-ylidene)hydrazinyl)quinoxalin-2(1*H*)-one (**11**) (in excellent yields at 400 W within 2 min). The microwave assisted synthesis of isatin-based quinoxaline **11** is shown in Scheme 2 (13, 87).

(iii) In another study, microwave assisted reaction of 3-acetyl-2*H*-chromen-2-one derivatives and cyclohexanone derivatives with the earlier prepared 3-hydrazinoquinoxaline (**10**) led to the formation of hydrazones 3-(2-(1-(6-substituted-2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazinyl)quinoxalin-2(1*H*)-one (**12**) and 3-(2-(2-substitutedcyclohexylidene)hydrazinyl)quinoxalin-2(1*H*)-one (**13**), resp., as expected. Formation of hydrazones **12** and **13** is shown in Scheme 3 (88).

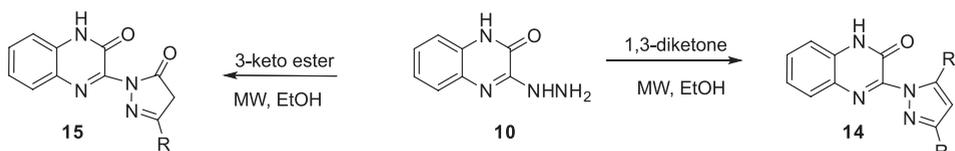
(iv) 3-Hydrazinoquinoxaline (**10**) was also used in earlier microwave assisted organic synthesis (MAOS) to validate its facile condensation with 1,3-diketone and  $\beta$ -keto ester to produce 3-(3,5-disubstituted-1*H*-pyrazol-1-yl)quinoxalin-2(1*H*)-one (**14**) and 3-(3-substituted-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)quinoxalin-2(1*H*)-one (**15**), resp., as shown in Scheme 4 (87, 89).



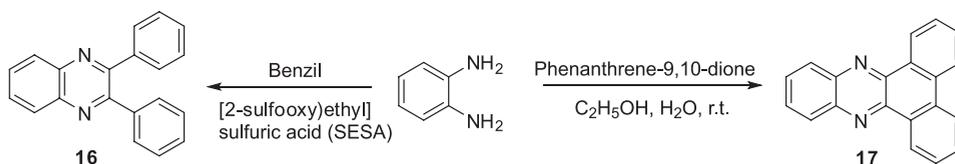
Scheme 2



Scheme 3



Scheme 4



Scheme 5

(v) Design of a method essential for the synthesis of a quinoxaline-based candidate *via* the one-pot approach using [2-(sulfoxy)ethyl]sulfuric acid (SESA) was achieved as shown in Scheme 5 (90). When benzil was used as a dicarbonyl synthon, 2,3-diphenyl quinoxaline (16) was obtained, whereas utilization of phenanthrene-9,10-dione as dicarbonyl agent afforded dibenzo[*a,c*]phenazine (17) as shown in Scheme 5 (90).

## ANTICANCER EFFICACY OF QUINOXALINES

### Quinoxaline screened for various cancer treatments

**Lung cancer.** – From the class of quinoxaline scaffold screened against lung cancer cell lines, compound **18** exhibited promising activity as inhibitor of the Wnt/b-catenin signal route with  $IC_{50}$  of 0.905 nmol L<sup>-1</sup> (91). The lung cancer cell HOP-92 showed no growth in the presence of compound **19** at  $1.0 \times 10^{-5}$  mol L<sup>-1</sup> (92). Compound **20** was also documented to bring about growth inhibition in drug resistant cancerous cell lines of lung cancer (93) (Fig. 4).

**Leukemia.** – Series of quinoxalines were reported to show growth inhibitory activity against the leukemia cell lines HL-60 (with 75 % of  $GI_{50}$  values as low as 0.01 to 0.15  $\mu$ mol L<sup>-1</sup>) (94).

However, compound **21** was the most active against the SR leukemia cell line with  $IC_{50}$  < 0.01  $\mu$ mol L<sup>-1</sup> (94, 95). Compound **22**, possessing 3,4,5-trimethoxyanilino pharmacophore

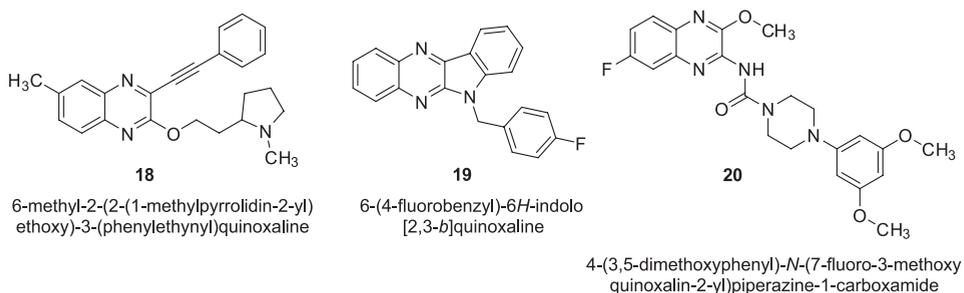


Fig. 4. Selected quinoxalines with promising activity in lung cancer treatment.

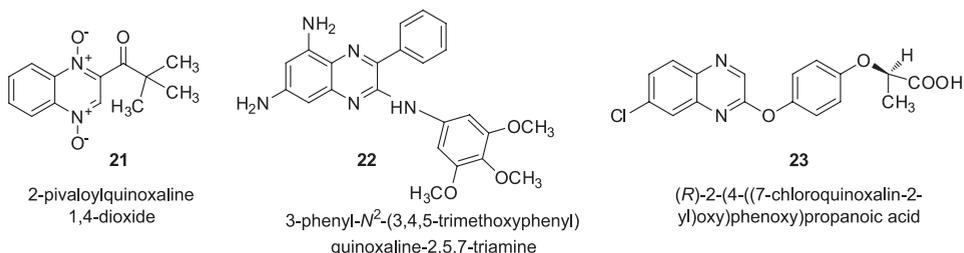


Fig. 5. Selected quinoxalines with promising activity in leukemia treatment.

at position 2 of the ring system, exhibited inhibition of leukemia cell lines HL-60 and MOLT-4 at nanomolar concentrations (95, 96). 2-Oxypropionic acid framework played a significant role in improving antitumor activity observed in quinoxaline template **23** against the leukemia cell line HL-60 (96) (Fig. 5).

**Colorectal cancer.** – Compound **24** was highly potent against three colon cancer cell lines: HCT 116 p53+/, HCT p53-/- and HT 29 with their respective  $IC_{50}$  of  $0.40 \pm 0.01$ ,  $0.30 \pm 0.07$  and  $0.30 \pm 0.06 \mu\text{mol L}^{-1}$  (97). Tricyclic quinoxaline **25** was reported to inhibit the growth of LS174T colon cancer cells with  $IC_{50}$  of  $4.12 \pm 0.67 \mu\text{mol L}^{-1}$  and it was well tolerated without apparent side effects (98). Out of the library of quinoxaline derivatives, substituted dihydroquinoxalin-2-one (**26**), synthesized from a copper-catalyzed coupling reaction, was the most potent with  $IC_{50}$  of  $4.96 \mu\text{mol L}^{-1}$  against the HeLaS3 cancer cell line (99) (Fig. 6).

**Breast cancer.** – Breast cancer is most common in mature female populations worldwide (100). According to a study, the quinoxaline derivative **27** inhibited the growth of breast cancer neoplasms and over 50 tumor cell lines (101). Quinoxaline-1,4-dioxide **28** was reported to stop abnormal growth in breast cancer cell lines with enhanced efficacy (102). Compound **29** showed remarkable efficiency against the breast cancer cell line MCF-7 as well as in skin related carcinogenesis based on *in vivo* investigation in mice (103) (Fig. 7).

**Liver cancer.** – All newly synthesized compounds were investigated on the human liver cell line (HEPG2). Compound **30** emerged as the most potent of this series with  $IC_{50}$

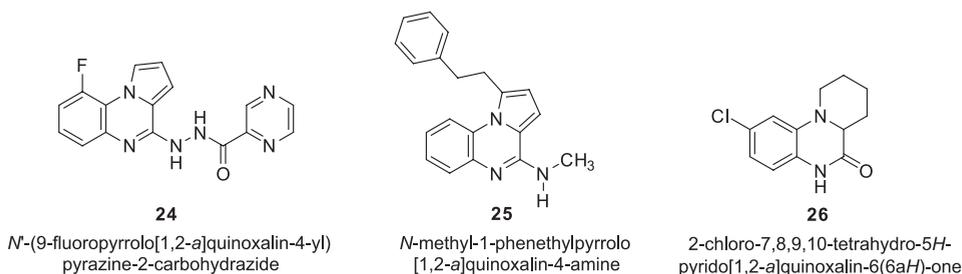


Fig. 6. Selected quinoxalines with promising activity in colorectal cancer treatment.

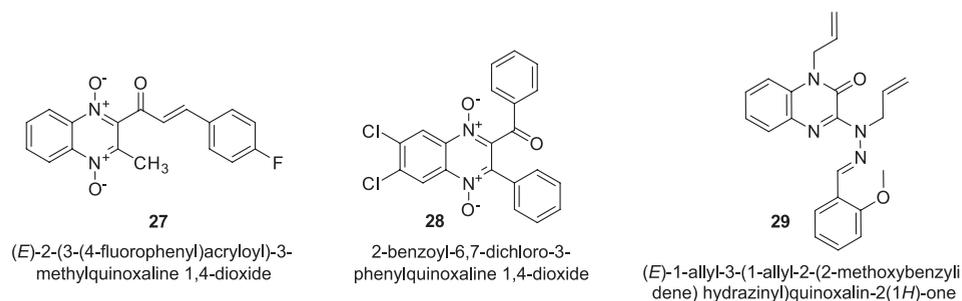


Fig. 7. Selected quinoxalines with promising activity in breast cancer treatment.

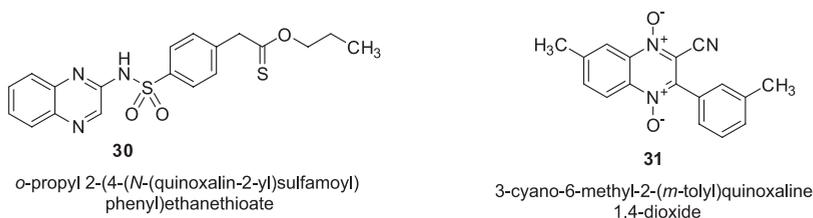


Fig. 8. Selected quinoxalines with promising activity in liver cancer treatment.

of 4.29  $\mu\text{mol L}^{-1}$  (104). Quinoxaline motif **31** was reported to be potent against HEPG2 at  $IC_{50}$  of 1.76  $\mu\text{mol L}^{-1}$  (Fig. 8) according to a preliminary mechanism study (105). Degrees of dT-QX cytotoxicity, TYMP and TK1 proteins have been reported as good indicators of high anticancer activity of the thymine analogue of dT-QX, whose structure (**32**) is shown in Fig. 9 (6). The result of the cell viability 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on four human liver cell lines was as shown in Fig. 9b, wherein the liver cell line HL-7702 exhibited the highest % cell viability followed by Bel-7402 and the cell line with the lowest % cell viability in MTT assay was Hep3B.

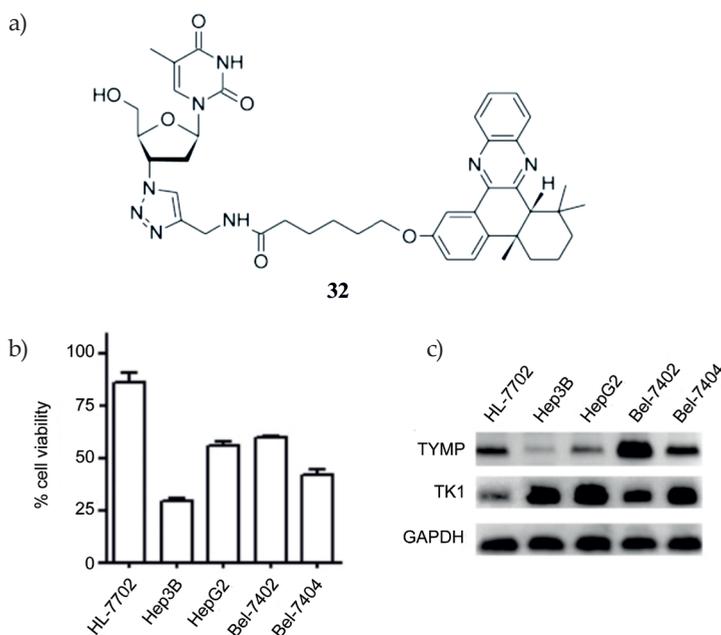


Fig. 9. Selected quinoxaline with promising activity in liver cancer treatment. Levels of dT-QX cytotoxicity and cellular TYMP and TK1 proteins in human liver cell lines. a) Chemical structure of thymidine analog dT-QX (**32**). b) Cell viability MTT assay on human liver cell lines including HL-7702, Hep3B, HepG2, Bel-7402 and Bel-7404 after treatment of dT-QX at 50  $\mu\text{mol L}^{-1}$  for 24 h (mean  $\pm$  SEM,  $n = 3$ ). c) Western blot analysis of TYMP and TK1 protein expression in HL-7702, Hep3B, HepG2, Bel-7402 and Bel-7404 liver cells (from ref. 6, with permission).

## STRUCTURE-ACTIVITY RELATIONSHIP STUDY (SAR)

The versatile activities of quinoxaline 1,4-di-*N*-oxides (QdNOs) are closely related to their chemical structures. The two *N*-oxide groups in the quinoxaline ring are necessary for the antitumor potential (106). In 2-alkylcarbonyl-3-trifluoromethylquinoxaline-1,4-di-*N*-oxide derivatives, anticancer activity depends on the substituents in the carbonyl group. It improves in the order: ethyl < isopropyl < *tert*-butyl < phenyl-ones (107). SAR studies for QdNOs suggest that position C(2) of quinoxaline should be substituted by electron-withdrawing moieties, preferably by a nitrile or an aroyl, an ester, an *N*-substituted amide group or a short brominated alkyl chain, for enhanced anticancer activity (108). Position C(3) is most often substituted by a short alkyl chain (*e.g.*, CH<sub>3</sub>, CF<sub>3</sub>) or phenyl. Substitution of C(6) or C(7) of QdNOs by Cl, F, CF<sub>3</sub>, or OCH<sub>3</sub> is also advantageous in antitumor diversity (81).

## CONCLUSIONS

Adverse effects and causes of cancer and tumor related diseases are expatiated in the study. Quinoxalines have, indeed, brought about considerable improvement and encouragement to human efforts in the fight against cancer. In addition, exploration of quinoxaline systems is unavoidable owing to their wide therapeutic applications. The present overview has revealed how quinoxaline and its derivatives have been used to inhibit the growth of cancer and tumor cells. Hence, due to the vast array of information gathered in the applications of quinoxaline in oncology, it is a warfare arsenal that may be developed into therapeutically important new-generation anticancer agents and serve possible future drug discovery.

*Acronyms.* – ALL – acute lymphocytic leukemia, CQS – chloroquinoxaline sulfonamide, DNA – deoxyribonucleic acid, EMT – epithelial mesenchymal transition, HBV – hepatitis B virus, HCV – hepatitis C virus, IBX – *o*-iodoxybenzoic acid, IC – inhibitory concentration, MAOS – microwave assisted organic synthesis, MDR – multi-drug resistance, MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, NSCLC – non-small cell lung cancer, QdNOs – quinoxaline 1,4-di-*N*-oxides, QC – quinoxaline-2-carboxylic acid, RNA – ribonucleic acid, SAR – structure-activity relationship, SCLC – small cell lung cancer, TK1 – thymidine kinase 1, TYMP – thymidine phosphorylase, ZEB – zinc finger E-box binding homeobox

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