Abstract

Nitrogen-containing heterocycles belong to the most versatile and important compounds in medicinal chemistry and for sustainable and advanced materials. Among FDA-approved drugs, around 60% of unique small molecule drugs incorporate a nitrogen heterocycle.[1] *N*-heterocyclic compounds are essential components of organic light-emitting diodes and organic solar cells. Quinoxalines or benzopyrazines are a class of heterocyclic compounds accessible by straightforward syntheses, present in commercially available drugs and optoelectronic architectures.

In this work, quinoxaline-containing compounds were synthesized and analyzed regarding their potential uses in biology and materials science, focussing on nitrogen-rich and dimeric quinoxalines. Various tetrazolo[1,5-*a*]quinoxalines were synthesized and converted to 1,2,3-triazoloquinoxalines and novel triazoloimidazoquinoxalines *via* a modified CuAAC procedure. A previously unknown copper-catalyzed denitrogenative annulation process was described in this context. As tankyrase inhibitors, substituted tetrazolo[1,5-*a*]quinoxaline derivatives were assembled and tested in biological studies. Suitable tetrazolo[1,5-*a*]quinoxalines and 1,2,3-triazoloquinoxalines were fitted with electron-rich donor units to assemble donor-acceptor emitter structures. Their emissive properties were investigated and discussed regarding the effect of the tetrazole unit and the direction of the triazole linker. A donor-acceptor compound with a triazole linker was shown to display delayed fluorescence, whereas the other regioisomer did not possess this property. Moreover, metal complexes of selected 1,2,3-triazoloquinoxalines were formed, and the synthesis of quinoxaline dimers was investigated, both linked directly and *via* triazole functions.

1 Introduction

1.1 Quinoxalines

1.1.1 Synthesis and Reactivity of Quinoxalines

Quinoxalines are *N*-heterocyclic compounds with a vast spectrum of biological and materials-related applications. They are based on the annelation of a benzene ring to a pyrazine ring, hence also referred to as benzopyrazines.[2] Quinoxalines (**1**) can be classified as diazanaphthalenes and are isomers to the other three members of the benzodiazine subclass (Figure 1, **2**-**4**).[3] Quinoxalines rarely occur in nature and are mostly accessed synthetically. Naturally present quinoxalines include riboflavin (vitamin B_2, **5**)[4] as well as the peptide antibiotic Echinomycin[5] and 6-chloro-2-quinoxalinecarboxylic acid 1,4-dioxide (MSD-819, **6**),[6] both of which were isolated from *Streptomyces* strains.

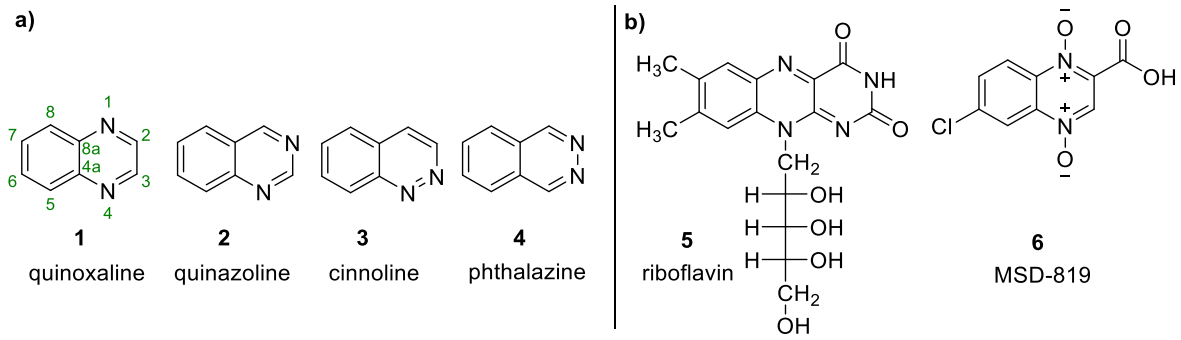
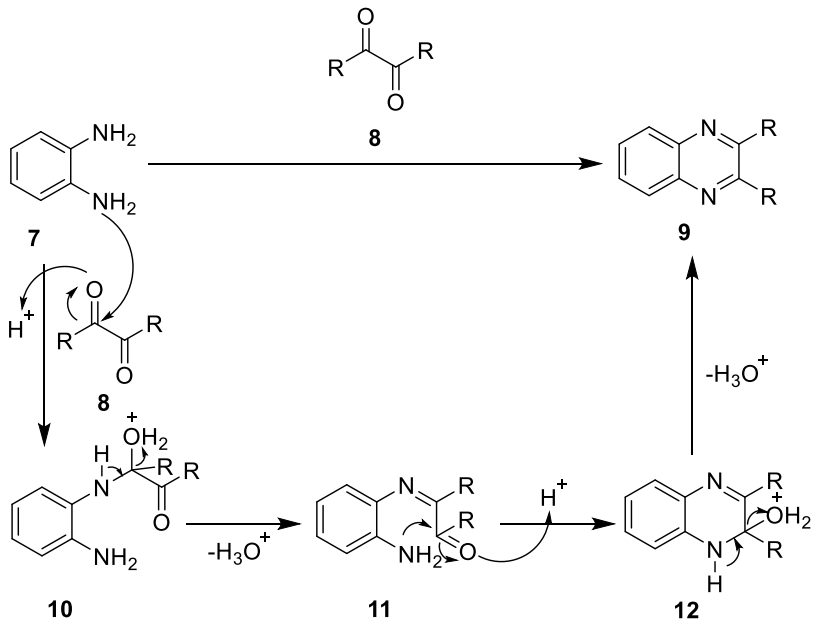


Figure 1: a) Quinoxaline (**1**) as a part of the benzodiazine class.[7] **b)** Naturally occurring quinoxaline derivatives: riboflavin (vitamin B_2)[4] and MSD-819, an antibiotic compound isolated from *Streptomyces* bacteria[6].

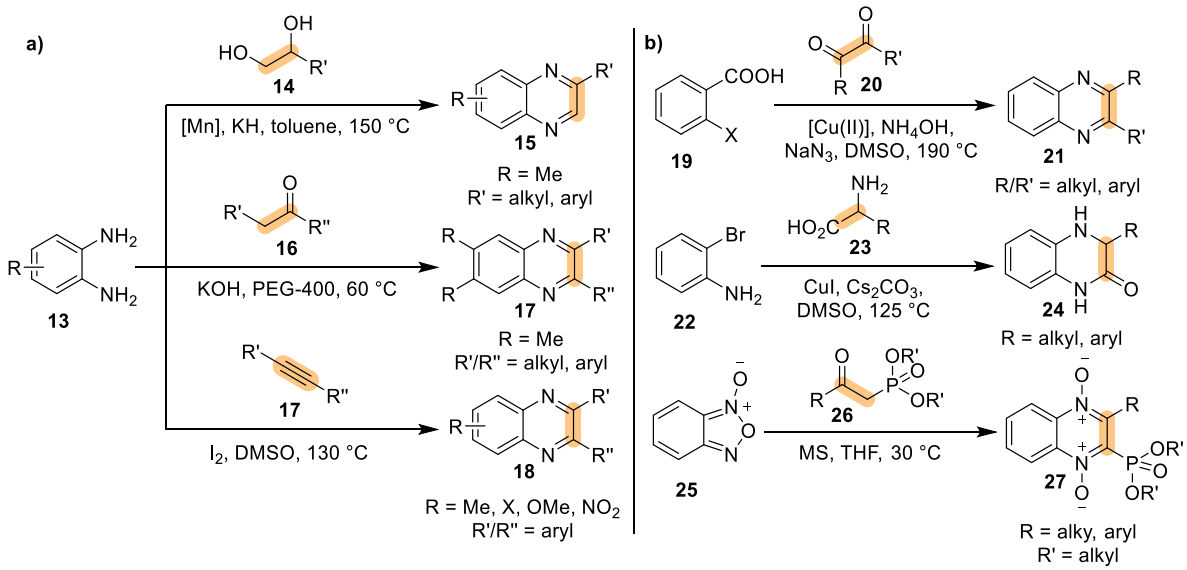
Their straightforward and fairly easy synthesis with high yields and outstanding stability in air distinguishes quinoxalines from other compounds with similar properties for biology and materials sciences.[8] The first synthetic access to quinoxalines was reported in 1844 by HINSBERG[9] *via* the condensation of aromatic diamines (**7**) with diketones **8** (Scheme 1). This method, often supported by Brønsted or Lewis acid catalysis, remains the most common approach to synthesizing quinoxalines.[10]
Further reported adaptions of this method allow for the use of a wide variety of readily available and reusable catalysts[11], the solvent-free synthesis of quinoxalines catalyzed by silver nanoparticles,[12] or the rapid synthesis under microwave irradiation[13].



Scheme 1: Synthesis of quinoxalines from 1,2-phenylenediamine **7** and a diketone (**8**) according to HINSBERG[9] and mechanism of the acid-catalyzed quinoxaline formation.[10]

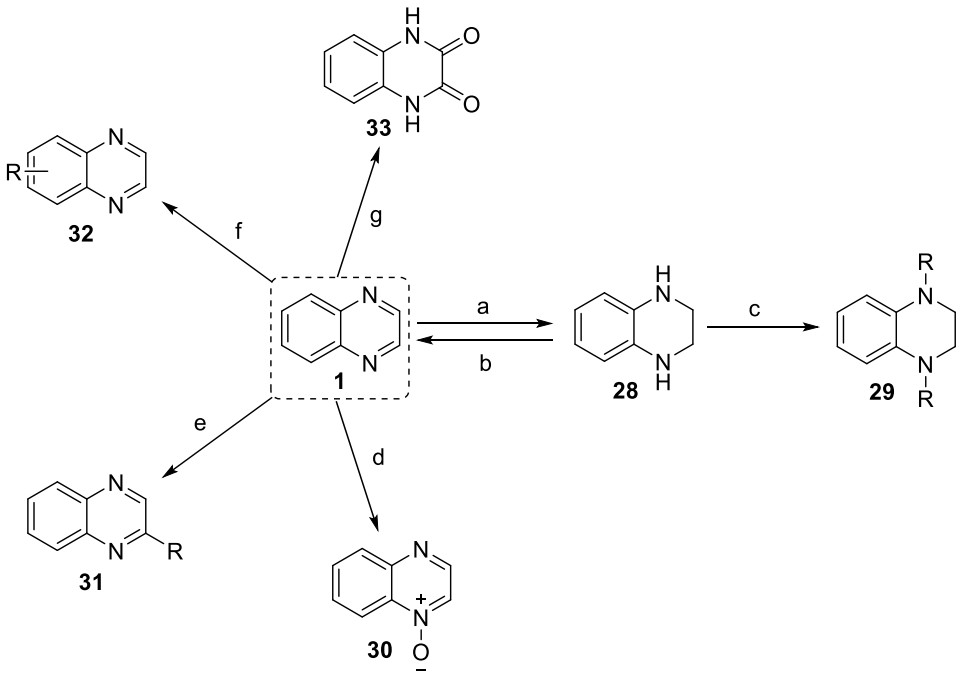
Other synthetic methods to obtain quinoxalines include the reaction of 1,2-diaminobenzenes with various two-carbon synthons such as alkynes,[14][15] ketones,[16] or vicinal alcohols[17] (Scheme 2a). Moreover, quinoxalines can be synthesized from aniline[18] or its derivatives, such as haloanilines[19] or nitroanilines[20]. Further precursors can be employed as well; 2-iodobenzoic acid can be converted in a SCHMIDT reaction,[21] or benzo[*c*][1,2,5]oxadiazole 1-oxide (**26**) can be subjected to a BEIRUT reaction[22] to obtain the target heterocycle (Scheme 2b).

Quinoxalines are weakly basic and electron-deficient heterocycles and only weakly susceptible to electrophilic aromatic substitutions.[10,23] Harsh conditions are necessary to conduct nitrations[24] or brominations[25] at the benzene carbon atoms of the quinoxaline system. Reactions on the pyrazine carbon atoms are easier to conduct[10,26,27], and especially haloquinoxalines are prone to react with nucleophiles.[28]



Scheme 2: a) Synthesis of quinoxalines from phenylenediamine derivatives **13** and two-carbon synthons.[14,16,17] **b)** Synthesis of quinoxalines from other aromatic precursors.[19,21,22]

Quinoxalines can be reduced to the corresponding 1,2,3,4-tetrahydroquinoxaline **28**, *e.g.*, using metal hydrides[29] or *via* palladium-catalyzed transfer hydrogenation.[30] The pyrazine nitrogen of dihydro- or tetrahydroquinoxaline compounds readily reacts as a nucleophile in alkylation reactions.[31,32] Tetrahydroquinoxalines can be re-oxidized to quinoxalines through dehydroaromatization with vanadium pentoxide[33]. Quinoxaline derivatives can be further oxidized to quinoxalinones (**33**)[34] or quinoxaline *N*-oxides (**30**)[35,36], depending on the conditions. The variety of reactions that can be conducted on the quinoxaline scaffold (Scheme 3) allows for easy modifications and enables these heterocycles to be used as a versatile building block in various applications.[8]



Scheme 3: General reactivity of quinoxalines (simplified): a: reduction, *e.g.,* with $LiAlH_4$[29] or $Pd(OAc)_2/B_2pin_2$[30], b: oxidation, *e.g.,* with V_2O_5/SiO_2[33], c: *N*-substitution, *e.g.,* with RX (R = alkyl/Bn, X = I, Br, Cl)/$CaCO_3$ or Na_2CO_3[31,32], d: *N*-oxidation, *e.g.*, with *m*-CPBA[36], e: heteroaromatic substitution, *e.g.,* zincation with $ZnCl_2/(TMP)_2Mg{\cdot}2LiCl$[26] or Minisci acylation with pyruvic aid and $FeSO_4/(NH)_4S_2O_8$[27], f: (electrophilic) aromatic substitution, *e.g.* bromination with Br_2 (R = Br)[25] or nitration with HNO_3/H_2SO_4 (R = NO_2)[24], g: oxidation, *e.g.* with [bis(trifluoroacetoxy)iodo]benzene[34]. For haloquinoxalines such as 2-chloroquinoxaline, nucleophilic substitution reactions, and various cross-coupling reactions are possible.[10]

1.1.2 Quinoxalines in Biology

Quinoxalines are widely used and researched for various biological applications. Several quinoxaline-based drugs are marketed (Figure 2), and five new quinoxaline-based drugs have been approved since 2017.[37] Brimonidine (**34**) is a quinoxaline-based α-adrenergic agonist used as an antiglaucoma drug against facial erythema of rosacea.[37] Varenicline (**37**), a drug for smoking cessation,[37] has been deemed an essential medicine by the World Health Organization in 2021.[38] Glecaprevir and Voxilaprevir are quinoxaline-based cyclic antiviral drugs against Hepatitis C, whereas Caroverine (**35**) is a spasmolytic drug used to treat tinnitus.[37] Erdatifinib (**36**) inhibited the fibroblast growth factor receptor and was approved as a novel "first-in-class" drug against bladder cancer by the U.S. FDA (Food&Drug Administration) in 2019, indicating its potential and usually a different mechanism of action from existing therapies.[37,39]

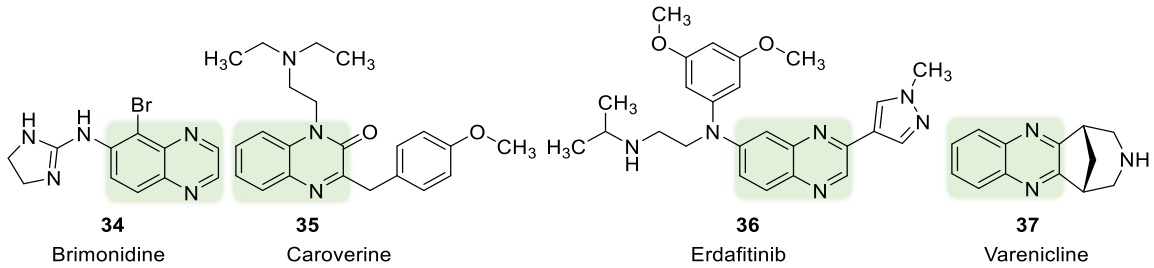


Figure 2: Quinoxaline-based drugs against glaucoma (**34**), tinnitus (**35**), bladder cancer (**36**), and for smoking cessation (**37**).[37]

Various quinoxaline derivatives have been reported to exhibit antibacterial [4,40,41–43] and antifungal[41,44] properties. Quinoxalines with antiviral activity range from the inhibition of *Flavivirus*[45], HIV[46], Ebola, and Marburg viruses[47] to combatting drug-resistant variants of Hepatitis C[48] and activity against the Potato Virus Y[49], highlighting their potential application in agriculture (see Figure 3). Natural quinoxaline-containing non-ribosomal peptides such as echinomycin, triostin A, and synthetic derivatives are studied for their anticancer activity.[5,50] Other quinoxalines with anticancer properties inhibit fibroblast growth factor receptors,[51] vascular endothelial growth factor receptors,[52] or enzymes such as MMP-9/MAO-A[53] and the transglutaminase 2[54]. Moreover, various quinoxaline derivatives can act as inhibitors of the Wnt/β-catenin pathway[54–56] or activate the Sirt6 protein deacylase[57,58]. Further biologically relevant quinoxalines show anti-convulsant[59], anti-inflammatory[60], anti-diabetic[61], antiparasitic[62] and anticoagulant[63] properties.

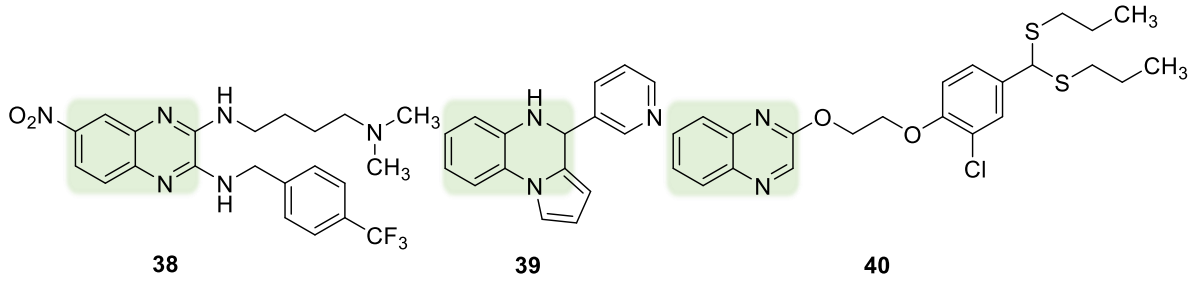


Figure 3: Quinoxalines with various biological functions: antibacterial activity against *Escherichia Coli* (**38**)[43], Sirt6 activation (**39**)[57], antiviral activity against Potato Virus Y (**40**)[49].

In addition to the multitude of quinoxalines with biological activity, they also play an important role in bioimaging and as biological probes (Figure 4). Quinoxaline-based fluorescent probes target the Golgi apparatus of cancer cells,[64] mitochondrial nucleic acids,[65] or detect cholesterol in human serum[66]. Quinoxaline derivatives can act as Tau protein and β-amyloid plaque imaging agents for detecting Alzheimer's disease.[67–69]

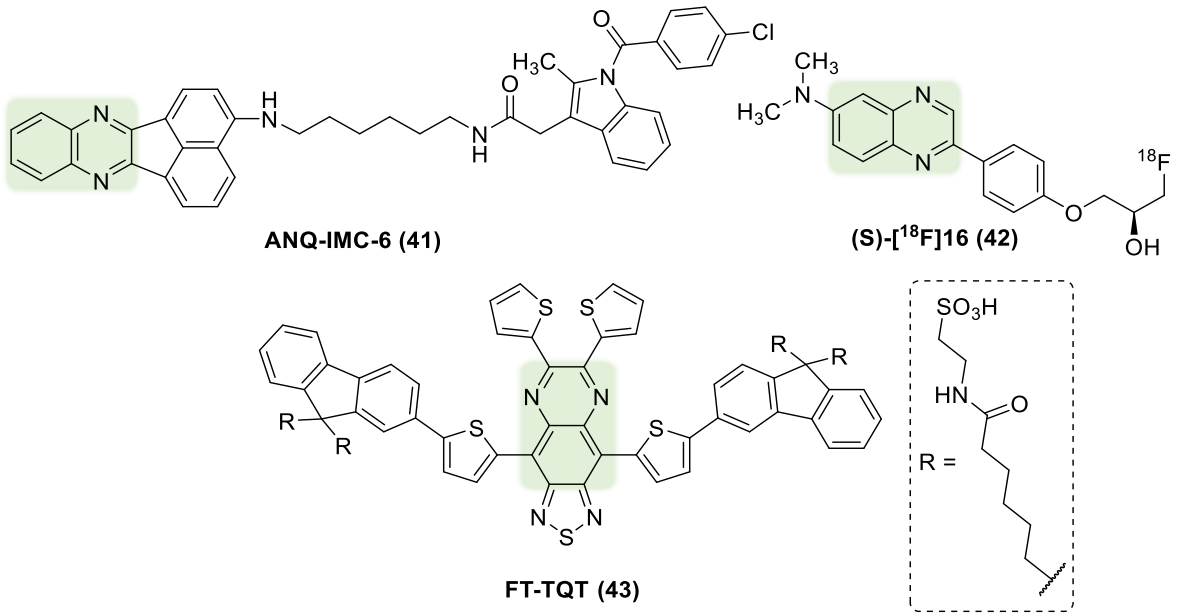


Figure 4: Quinoxaline-based fluorescent probes for targeting the Golgi apparatus of cancer cells (**41**)[64], as a potential Tau imaging agent for the diagnosis of Alzheimer's disease (**42**)[68] and as high-performance NIR-II dye (**43**)[70].

Water-soluble quinoxaline photosensitizers have been reported for use in bioimaging and photodynamic therapy,[71] and quinoxaline-based small-molecule dyes are promising compounds for NIR-II (second near-infrared window, 1000-1700 nm) fluorescence imaging[70,72]. Furthermore, organic nanoparticles and polymer dots (Figure 5) incorporating quinoxalines have attracted interest for application in *in vivo* biological imaging due to their ultrabright fluorescence and minimal toxicity.[73,74]

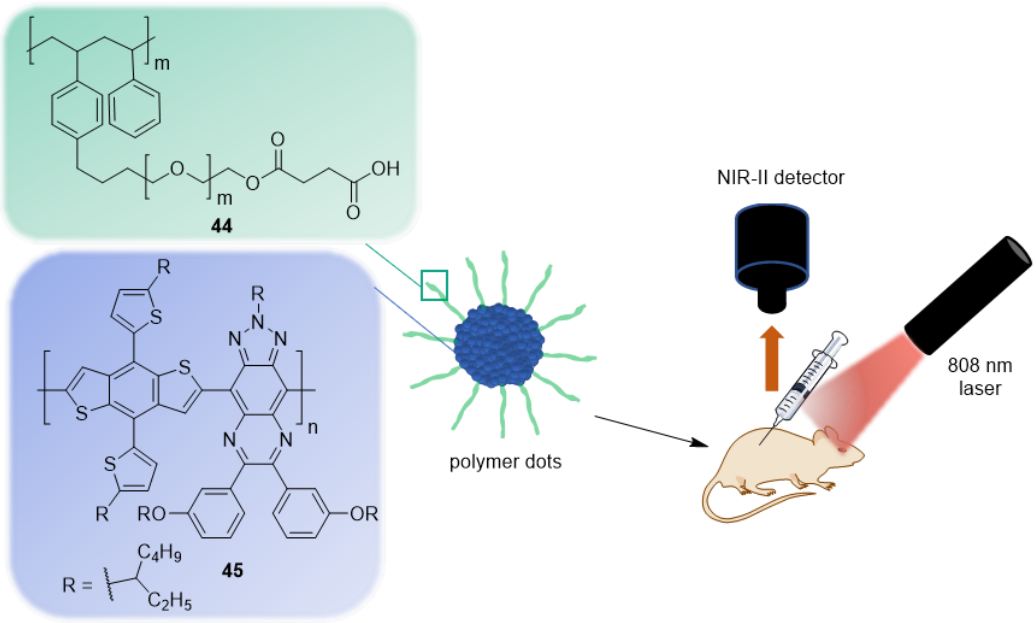


Figure 5: Quinoxaline-based semiconducting fluorescent polymer dots for *in vivo* NIR tumor imaging.[74]

1.1.3 Quinoxalines in Materials Sciences

Quinoxalines are not only relevant compounds in biology, but their scaffold is also a crucial building block for various materials-related purposes such as optoelectronics and photovoltaic applications. Organic solar cells (OSCs) and organic light-emitting diodes (OLEDs) are being investigated as highly promising technologies.[75,76] While OSCs are an important tool to fulfill future energy demands sustainably,[75] OLEDs can be used in flexible displays, offer high resolution and contrast, and are an energy-efficient alternative to liquid crystal displays (LCDs).[77]

Quinoxalines as electron-deficient *N*-heterocycles can be employed as an electron-acceptor unit in donor-acceptor (D-A) type systems, one of the most researched design approaches for optoelectronic applications.[8] Compounds based on the quinoxaline moiety are especially suitable for materials applications due to their straightforward synthetic accessibility, excellent stability in the air, and structure that allows for various structural modifications.[8] They show efficient light absorption and emission, high charge carrier mobility, and can easily be color-tuned.[78]

Quinoxaline-based polymers are currently some of the most highly researched materials for OSCs (Figure 6).[75,79–86] They are used in D-A copolymer donors (**46**) with up to 17.6% efficiency[75,85], as photosensitizers (**47**) in dye-sensitized solar cells with efficiencies of up to 13.2%,[79,87] and as hole-transporting material in perovskite solar

cells with efficiencies over 21%.[80,86] Quinoxaline-containing compounds have been reported to self-assemble to monolayers in sensitizers for OSCs[81], be part of alcohol-processable conjugated polymers,[82] and form double-cable conjugated polymers for single-component OSCs with 13% efficiency[83].

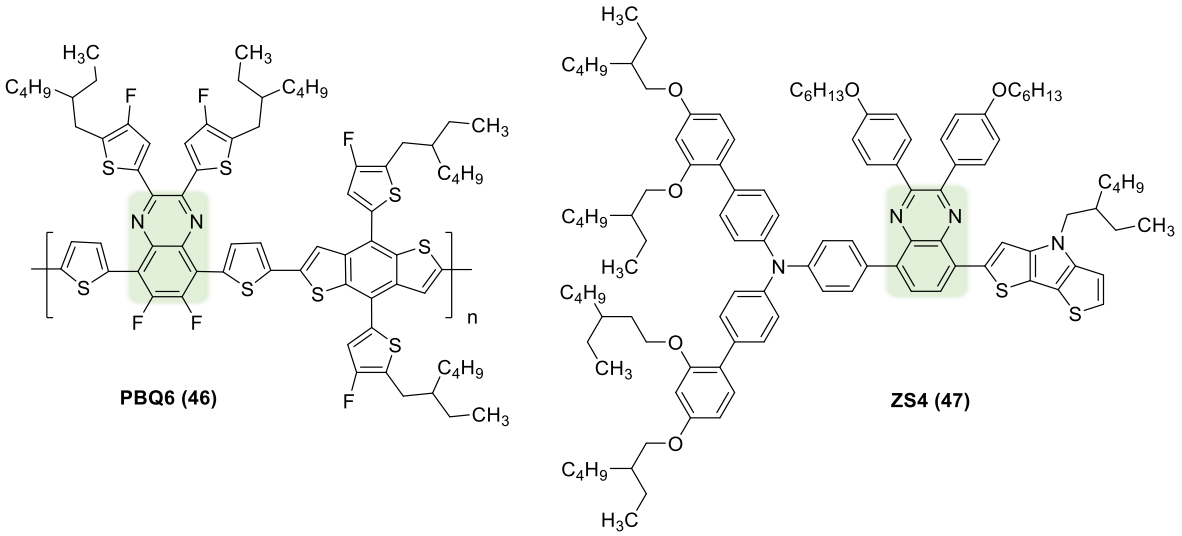


Figure 6: A quinoxaline-based donor-acceptor copolymer donor (**46**) for OSCs [85] and photosensitizer incorporating a quinoxaline moiety (**47**) in dye-sensitized OSCs[79].

Quinoxaline-based materials are also especially relevant for research and development in the field of OLEDs (Figure 7).[88–90] **HAT-CN** (1,4,5,8,9,11-hexaazatriphenylene hexacarbonitrile, **49**) is an established and commercially available hole transport and hole injection material used in many devices.[90,91] Various quinoxaline derivatives have also been reported to possess suitable properties for use in electron transport layers (see Figure 7 and Figure 8, **48, 51-53**).[89] Due to their additional imine nitrogen atom, they usually possess a higher electron affinity than related materials such as quinolines, hinting towards more favorable electron injection and transport abilities.[92] Especially polyquinoxalines, quinoxaline dimers, and phenylquinoxalines have been successfully investigated in the past with mobilities of up to 10^{-3} $cm^2V^{-1}s^{-1}$.[92–94]

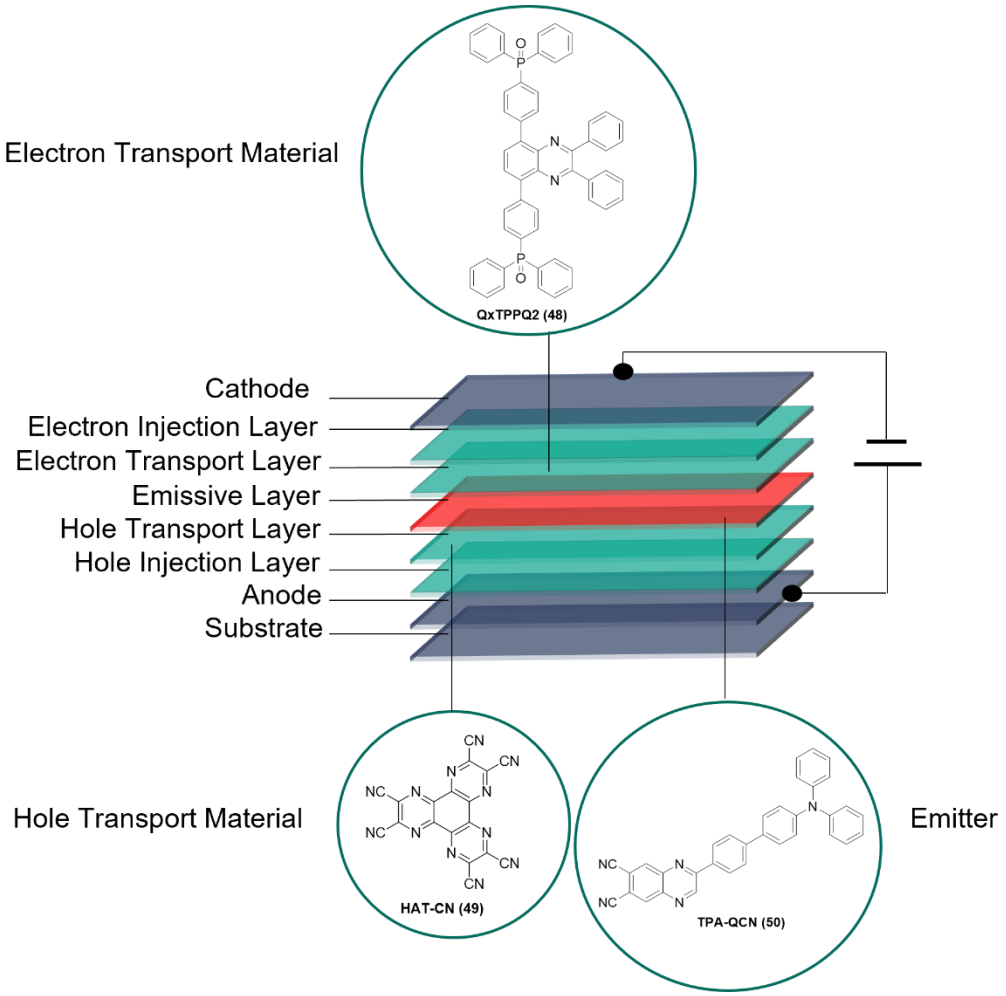


Figure 7: General stacked device structure of organic light emitting diodes (OLEDs) and exemplary applications of quinoxalines in OLED devices.[77,88–90]

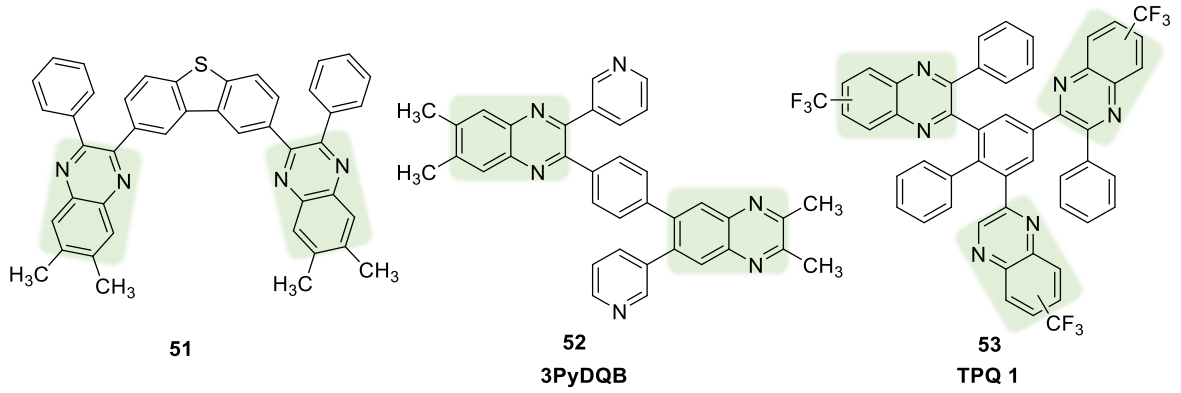


Figure 8: Quinoxaline-based materials **51**-**53** for electron transport layers.[93,95]

Moreover, quinoxaline cores are often used in emitter compounds for OLEDs, especially as electron-deficient acceptor moieties in donor-acceptor-type architectures.[76,78,96] Their use is not limited to conventional fluorescent[97] or phos-

phorescent[98] systems; a multitude of quinoxaline-based compounds have been shown to exhibit thermally activated delayed fluorescence (TADF) as well.[99–105] This process allows for 100% theoretical internal quantum efficiency (IQE) as the triplet excitons can be converted into singlet excitons *via* reverse intersystem crossing (RISC) and thus be harvested in a delayed fluorescence process from the S_1 state (see Figure 9).[106] One of the most important requirements for a molecule to exhibit TADF is a small singlet-triplet energy gap (ΔE_{ST}) that increases the RISC rate.[106]

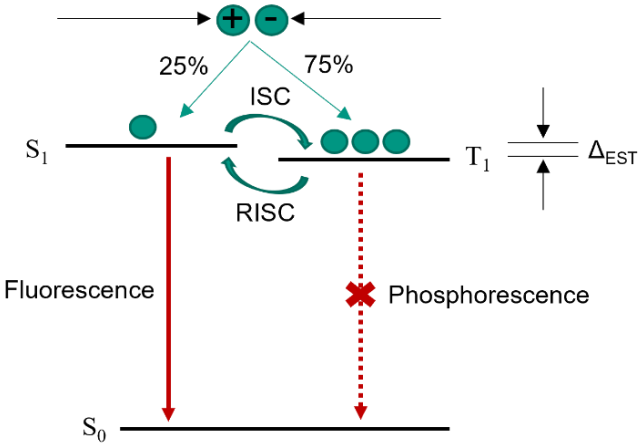


Figure 9: Simplified Jablonski Diagram for thermally activated delayed fluorescence.[106,107]

Quinoxaline-based TADF emitters are usually substituted with an electron-rich donor moiety like carbazole or diphenylamine on the pyrazine or benzene ring, often separated by a spacer such as a phenyl unit (see Figure 10).[100,102] The quinoxaline then acts as the electron-deficient acceptor unit. This design allows for a sterically induced separation of the HOMO and LUMO, leading to efficient charge transfer, while the phenyl linker reduces the HOMO and LUMO isolation to ensure high oscillator strengths and thus high photoluminescence quantum yields (PLQY).[106] Devices with selected TADF emitters containing quinoxaline acceptors display record-high external quantum efficiencies (EQE) of up to 30.3% for deep-red OLEDs[101] and 39.1% EQE for green OLEDs (**DQBC** (**56**), Figure 10)[99]. Solution-processed red TADF OLEDs with a quinoxaline acceptor show up to 16.7% EQE (***p*CNQ-TPA** (**54**))[100], devices with chiral quinoxaline-based TADF emitters enable circularly polarized luminescence with 28.3% EQE and yellow emission[108].