CHAPTER FIVE

Azoles and related derivatives

Contents

Azoles are a group of compounds that contain a five-membered ring with nitrogen and other atoms such as sulfur and oxygen. Although they possess a range of biological activities, they are especially known as antifungal agents commonly prescribed in clinical practice [1]. The azole ring system is chemically diverse comprising thiadiazole, oxadiazole, triazole, imidazole, isoxazole, pyrazole, and other chemically related rings. Thiadiazoles contains a five-membered ring system with a sulfur and two nitrogen atoms. Natural thiadiazoles exist in four isomeric forms 1,3,4-, 1,2,3-, 1,2,5-, and 1,2,4-thiadiazole. Derivatives of 1,3,4-thiadiazole are highly active compounds demonstrating antibacterial, antifungal, anticancer, anticonvulsant, antiinflammatory, antiviral, and antileishmanial properties [2].

The oxadiazole ring system comprises one oxygen and two nitrogen atoms. The forms of oxadiazoles include 1,3,4-, 1,2,3-, 1,2,5-, and 1,2,4-oxadiazole. Substituted oxadiazoles have been identified as antidiabetic, anticonvulsant, anti-HIV, anti-Alzheimer's, antimicrobial, antiinflammatory, immunosuppressant, and anticancer agents. The 1,3,4-oxadiazole ring system

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has also been studied for its role in enzyme inhibition targeting cancer and other diseases. In this regard, derivatives of 1,3,4-oxadiazole have been reported to inhibit telomerase, methionine aminopeptidase, histone deacetylase, focal adhesion kinase, and thymidylate synthase enzymes [3].

Triazoles contain a five-membered ring system with three nitrogen and two carbon atoms. The isomeric forms of triazole, primarily conjugated with heterocyclic derivatives, exhibit diverse chemical and biological properties making them promising for drug development and other applications. The two tautomeric forms of the triazole ring namely 1,2,3-triazole and 1,2,4-triazole have attracted attention of the drug development community since they are promising for treatment of a variety of diseases. The ^{1}H and ^{4}H-1,2,4-triazole derivatives have been studied on a number of clinically important targets due to their interesting biological activity profile. The 1,2,4-triazole ring system, incorporated into antimicrobial, antiinflammatory, antimigraine, and CNS stimulatory drugs and their candidates, has been thoroughly studied. Examples include antimycotic drugs such as voriconazole, itraconazole, and fluconazole, anticonvulsant drugs such as estazolam, and antiviral drugs such as ribavirin. Triazole derivatives possess a wide range of biological activities, therefore, they are of focal interest in drug development. A number of 1,2,4-triazole-3-thione and 1,2,4-triazole-3-(4*H*)-thione derivatives have shown to exert promising *in vivo* activities including anticonvulsant, antidepressant, antibacterial, antiviral, anticancer, antifungal, antiinflammatory, analgesic, and antioxidant activities [4].

The biological activity profile of azoles and related derivatives also includes α-glucosidase inhibition. The scientific literature has witnessed a number of reports on azoles exhibiting promising inhibition of the enzyme. This chapter discusses promising azole derivatives and related compounds identified as α-glucosidase inhibitors.

5.1 Thiadiazoles, oxadiazoles, and triazoles

Kashtoh et al. [5] reported synthesis of a series of thiadiazole and oxadiazole derivatives. Although majority of the compounds showed moderate inhibition of yeast α-glucosidase, three oxadiazoles (**1**−**3**) and two thiadiazoles (**4** and **5**) are noteworthy to mention (Fig. 5.1). The former are all noncompetitive inhibitors ($K_i = 12$, 4.36, and 11.2 μM, respectively) whereas the latter are each competitive and noncompetitive inhibitors ($K_i = 6.0$ and 14.3 μM, respectively). The activity of the compounds is primarily dependent on the oxadiazole and thiadiazole moieties, the carbonyl oxygen and the substitutions on the aromatic rings.

The yeast α-glucosidase inhibitory profile of benzothiazole compounds containing the benzohydrazide moiety is also similar to that of thiadiazoles, especially for the compounds **6**, **7**, and **8** ($IC_{50} = 5.55$, 5.58, and 5.31 μM, respectively) (Fig. 5.2). Molecular docking showed strong binding affinity of the compounds to the *C*-terminal domain of α-glucosidase with no significant correlation of binding energies to IC_{50} values. Compounds bearing higher dipole moment and weaker hydrogen bonding interactions displayed lower inhibitory activity [6].

Recently, the synthetic diamine-bridged coumarinyl oxadiazole conjugates have shown to potently inhibit α-glucosidase ($IC_{50} = 0.07-0.76$ μM) [7]. The conjugates were synthesized using three different types of linkers namely phenylenediamine, benzidine, and 4,4′-oxydianiline. Generally, compounds from all the series displayed comparable inhibition of the enzyme. Compound **9** ($IC_{50} = 0.07$ μM) with the 4,4′-oxydianiline linker and the *meta*-bromo substitution on the aryl ring highest affinity to the enzyme in the series. Moreover, compounds possessing the phenylenediamine

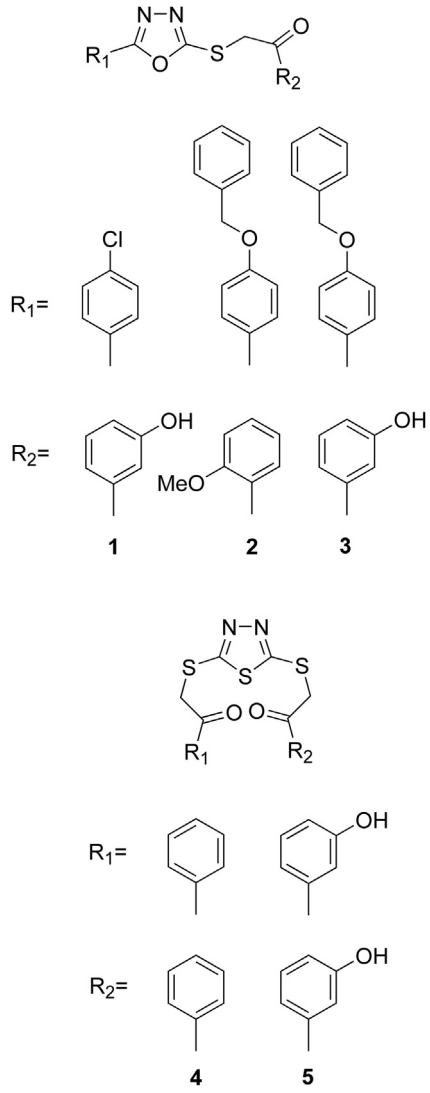

Figure 5.1 The thiadiazole and oxadiazole inhibitors of α-glucosidase. *Reproduced from U. Ghani, Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: finding needle in the haystack, Eur. J. Med. Chem. 103 (2015) 133–162.*

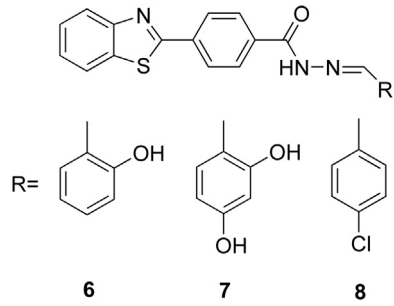

Figure 5.2 Benzothiazole derivatives containing the benzohydrazide moiety. *Reproduced from U. Ghani, Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: finding needle in the haystack, Eur. J. Med. Chem. 103 (2015) 133–162. © 2015 French Société de Chimie Thérapeutique published by Elsevier Masson SAS. All rights reserved.*

linker also exhibited promising activity including the ones bearing electron-poor and electron-rich substituents ($IC_{50} = 0.11–2.18\ \mu M$). The position and the type of substituents played a central role in the activity. Conjugates containing the benzidine linker inhibited the enzyme with an IC_{50} range of $0.11–0.76\ \mu M$. Conjugates bearing the 4,4′-oxydianiline linker exhibited relatively higher level of inhibition potency. These include compound **10** ($IC_{50} = 0.09\ \mu M$) carrying a methyl group at the *para*-position of the aryl ring, and compound **11** ($IC_{50} = 0.09\ \mu M$) carrying a chloro substituent at the *ortho* and *para*-positions of the aromatic ring (Fig. 5.3).

A series of 4-substituted 1,2,3-triazoles conjugated with D-xylose, D-galactose, D-allose, and D-ribose sugars have been synthesized and screened for yeast maltase inhibitory activity. Compound **12**, a β-D-ribosyl triazole, exhibited highest potency among other derivatives studied ($IC_{50} = 3.8–24.7\ \mu M$) (Fig. 5.4). Molecular docking suggested that the target inhibitors bind to the enzyme active site by mimicking the transition state of the substrate. Moreover, the role of the N_3 atom in the

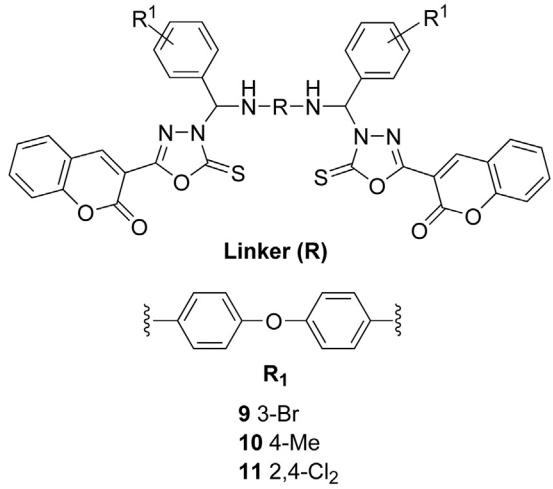

Figure 5.3 The diamine-bridged coumarinyl oxadiazole conjugates. Compounds possessing the phenylenediamine linker exhibited potent activity including the ones bearing electron-poor and electron-rich substituents.

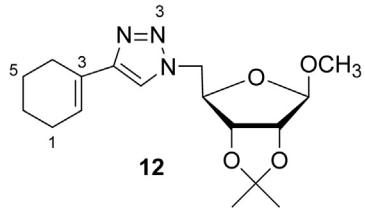

Figure 5.4 β-D-Ribosyl triazole: computational studies show that it acts as a transition state analog of α-glucosidase substrate. *Reproduced from U. Ghani, Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: finding needle in the haystack, Eur. J. Med. Chem. 103 (2015) 133–162.*

triazole ring and the R_2 substituent is also important. Oral administration of some of these triazoles to normal rats also suppressed postprandial glucose levels [8].

Wang et al. [9] synthesized and evaluated a series of 5,6-diaryl-1,2,4-triazine thiazole derivatives as α-glucosidase

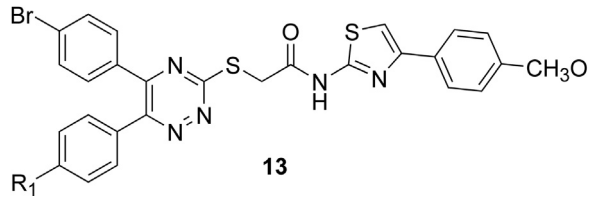

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Figure 5.5 The 5,6-diaryl-1,2,4-triazine thiazole derivatives. Manipulation of R_1 substitution especially incorporation of electron-withdrawing groups such as fluorine or bromine yielded potent inhibitors of α-glucosidase.

inhibitors. Compound **13** ($IC_{50} = 2.8$ μM) bearing an R_1 bromine and an R_2 methoxy group exhibited highest level of enzyme inhibition (Fig. 5.5). A general comparison of the activities showed that incorporation of electron-withdrawing groups such as fluorine or bromine at R_1 position enhanced the level of inhibition. Therefore, the type of substitution at R_1 position has greater influence on α-glucosidase inhibition than the one at R_2.

5.2 Other related derivatives

5.2.1 Oxindoles

Synthesis and evaluation of oxindole derivatives for yeast α-glucosidase inhibitory activity have identified compounds **14**, **15**, and **16** ($IC_{50} = 2.71$, 11.41, and 14.2 μM, respectively) (Fig. 5.6). Molecular docking using a model of yeast α-glucosidase suggested that the oxindole moiety optimally fits into the active site pocket of the enzyme allowing important interactions with corresponding residues [10].

Luthra et al. synthesized a library of oxindole derivatives by scaffold hopping of known α-glucosidase inhibitors namely synthetic oxindole, natural piperidine and cytidine, and

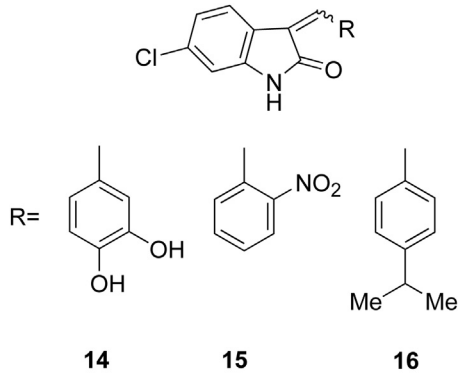


Figure 5.6 The oxindole α-glucosidase inhibitors. *Reproduced from U. Ghani, Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: finding needle in the haystack, Eur. J. Med. Chem. 103 (2015) 133–162. © 2015 French Société de Chimie Thérapeutique published by Elsevier Masson SAS. All rights reserved.*

pyridofuranone derivative [11]. The final compounds displayed promising α-glucosidase inhibitory activity with an IC_{50} range of 0.64–10.22 μM (Fig. 5.7). Compound **17** was 3–4 fold more potent than its precursors that were initially used to design the library. The structural motifs in these compounds apparently responsible for α-glucosidase inhibition include the indole moiety, pyridine ring, and the amide group. Also, the C_5 fluoro substitution of the indole ring enhances the potency of inhibition as in compound **17** (a competitive inhibitor), which is three-fold more potent than the compounds **18** and **19**. In contrast, the compounds containing the nitro group (as in **20**) displayed less potency of inhibition probably due to its strong electron-withdrawing properties. Compounds **18** and **21** with amide moieties (pyrrolidine and piperidine) also showed promising enzyme inhibition.

5.2.2 2-Arylquinazolin-4(3*H*)-one derivatives

The yeast α-glucosidase inhibitory activity of 2-arylquinazolin-4(3*H*)-one derivatives is primarily dependent on the

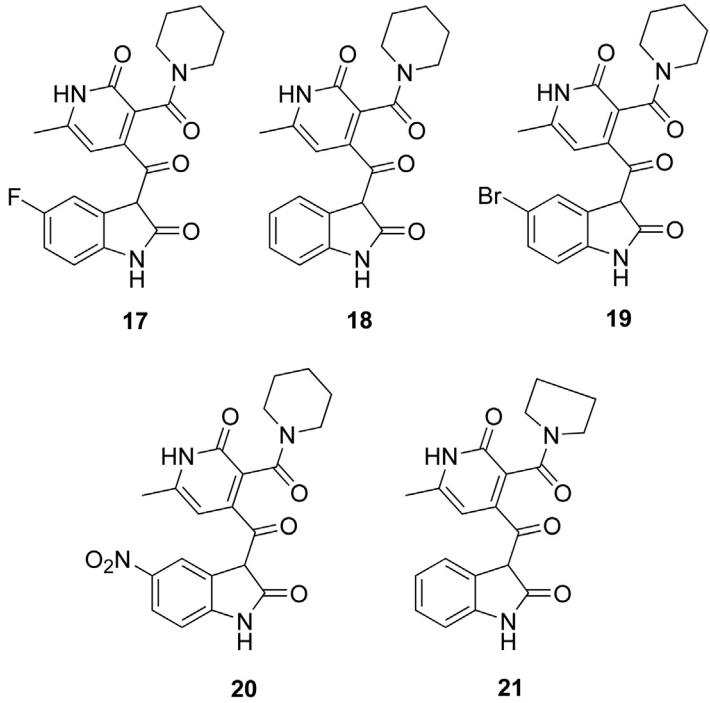


Figure 5.7 The oxindole derivatives synthesized by scaffold hopping of known α-glucosidase inhibitors such as synthetic oxindole, natural piperidine, cytidine, and pyridofuranone derivatives. The indole moiety, pyridine ring, and amide group are the structural motifs responsible for α-glucosidase inhibition.

2-arylquinazolin-4(3*H*)-one skeleton and the benzene ring at C_2 which is substituted with various electron-donating and withdrawing structures. Compound **22**, a competitive inhibitor of the enzyme and the most potent in the series, carries ethoxy and hydroxyl groups at C_3' and C_4' positions of the phenyl ring, respectively ($IC_{50} = 0.3\ \mu M$; $K_i = 0.43\ \mu M$) (Fig. 5.8). In this compound, presence of the two groups is essential for promising enzyme inhibition.

Compound **23** showed activity similar to that of **22** despite being substituted with only one methoxy group at C_4' position ($IC_{50} = 0.4\ \mu M$). However, it inhibited the enzyme

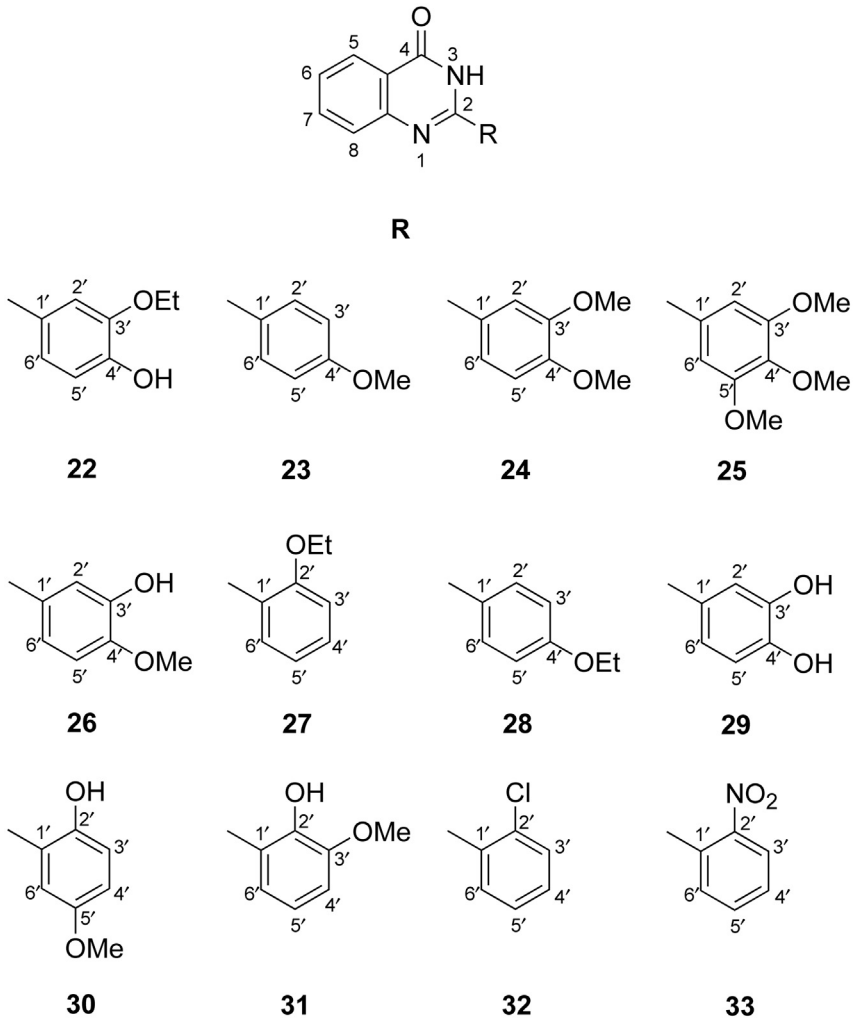


Figure 5.8 The activity of arylquinazoline derivatives primarily depends on their 2-arylquinazolin-4(3*H*)-one skeleton and the benzene ring at C_2 position, substituted with various electron-donating and withdrawing groups.

noncompetitively ($K_i = 0.25$ μM). When substituted with one more methoxy group at C_3' position (as in compound **24**), the activity was compromised by two-fold relative to that of **23** ($IC_{50} = 0.86$ μM; competitive inhibition, $K_i = 0.28$ μM).

Addition of one more methoxy group at C_5' position resulted in a significant loss of inhibitory activity as shown by compound **25** ($IC_{50} = 118$ μM). Replacement of the C_3' methoxy group of compound **24** with a hydroxyl group (as in **26**) suppressed its activity by almost two-fold ($IC_{50} = 1.9$ μM). Since the C_3' ethoxy group partly plays an important role in enabling the compound **22** to exhibit highest affinity to the enzyme, the activity profiling of other positions of the ethoxy group in the same benzene ring would be worth exploring. Example in this regard includes compound **27**, a mixed-type inhibitor substituted by an ethoxy group at C_2' rather than C_3', that also showed promising activity ($IC_{50} = 0.57$ μM; $K_i = 6.6$ μM).

In contrast, the C_4' ethoxy substitution in **28** drastically compromised its activity ($IC_{50} = 3.25$ μM). Interestingly, the dihydroxy substitution at C_3' and C_4' positions also afforded a potent inhibitor, that is, **29** ($IC_{50} = 1.5$ μM). Generally, the dihyroxy-substituted compounds tend to be more potent inhibitors than their monohydroxy counterparts. Moreover, the proportion of the distance between the methoxy and hydroxyl groups also contributed to the activity. Compound **30** ($IC_{50} = 1.15$ μM), which is substituted by the hydroxyl and ethoxy groups at C_2' and C_5', respectively, exhibited more potency than **31**, which is substituted by the same groups at C_2' and C_3', respectively ($IC_{50} = 14.6$ μM).

The chlorine analogs studied in the series also exhibited promising inhibitory activities. Chlorine and nitro substitutions at C_2' position of the phenyl ring were found to be most optimal for the activity within the series as observed in compounds **32** and **33** ($IC_{50} = 1.3$ and 1.45 μM, respectively) [12].

5.2.3 *Bis*-Indolylmethanes

Bis-Indolylmethanes naturally exist as metabolites in a wide range of plant species with aromatase inhibitory effects for cancer treatment, antimicrobial, and anti-HIV activities. They

possess therapeutic effects on estrogen metabolism in humans, and are used for treatment of fibromyalgia and irritable bowel disease [13]. Recently, a series of synthetic *bis*-indolylmethane sulfono-hydrazide derivatives have been identified as α-glucosidase inhibitors ($IC_{50} = 0.1-5.1$ μM) [13]. The activity of the compounds, bearing chloro groups at the phenyl ring, is mainly influenced by their number and position. Same applies to the nitro group-containing compounds in which the α-glucosidase inhibitory activity is mainly driven by the position of the nitro group. The structure and activity details of the compounds are cited in the original article [13].

5.2.4 Metallophthalocyanines

Macrocyclic compounds such as phthalocyanines have multiple applications in clinical, biomedical and analytical devices and procedures including gas sensors, catalysts, electrochromic devices, photosensitizers, and photodynamic cancer therapy [14]. Derivatives of phthalocyanine-containing aminopyrazole moieties are of interest in medicinal and pharmaceutical chemistry due to their wide spectrum of biological activities including antimicrobial activity [14]. Moreover, latest work on the aminopyrazole-substituted metallophthalocyanines has shown that they inhibit α-glucosidase in nanomolar range ($IC_{50} = 2.15-11.01$ nM/$K_i = 1.55-10.85$ nM). The compounds demonstrated much higher potency of α-glucosidase inhibition than that of acarbose especially the phthalonitrile derivative (**34**; $IC_{50} = 11.01$ nM/$K_i = 10.85$ nM) and its metal complex chloromanganese(III) phthalocyanine (**35**; $IC_{50} = 2.15$ nM/$K_i = 1.55$ nM), as shown in Fig. 5.9.

5.2.5 Thiobarbiturates

Barbiturates or malonylurea compounds are commonly used as anesthetics, and for treatment of epilepsy, anxiety, and psychiatric diseases. Similar to thiouracil, they carry various

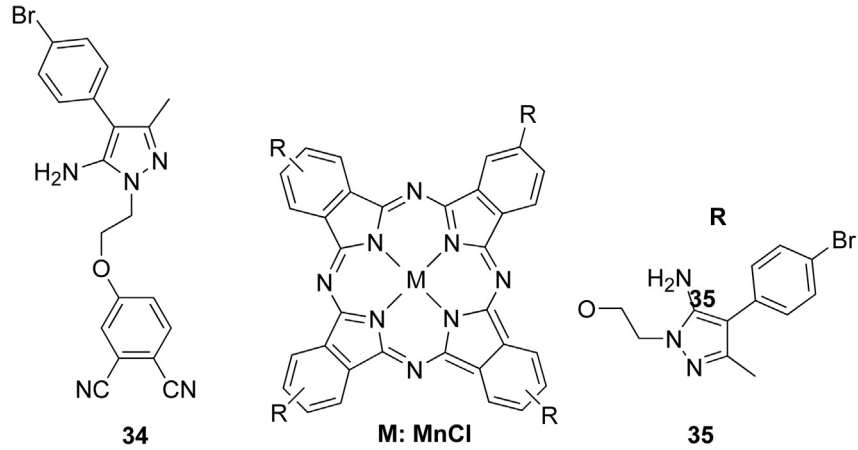
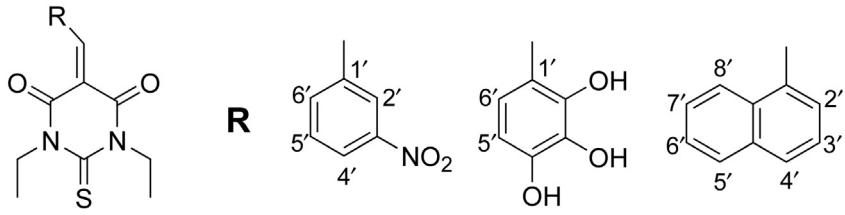


Figure 5.9 The aminopyrazole-substituted metallophthalocyanines inhibit α-glucosidase in nanomolar range.

substituents at C_5 position which influence their activity and lipid solubility [15]. The effects of the C_5 substitution on yeast α-glucosidase inhibitory activity have been explored using various synthetic 5-arylidene-*N*,*N*′-diethylthiobarbituric acid derivatives [15]. The compounds exhibited varying degree of enzyme inhibition with noticeable activities by compounds **36**, **37**, and **38** (Fig. 5.10). Compound **37**, the most potent in the series ($IC_{50} = 0.6$ nM), is a noncompetitive inhibitor carrying three hydroxyl groups at the 2′, 3′, and 4′ positions. It appears that these hydroxyl groups are essential for activity since compounds containing the hydroxyl groups either at 3′ and 4′ positions or at 4′ position alone markedly displayed weak inhibitory activities. Compound **38**, with a naphthyl substitution, showed more potency of inhibition ($IC_{50} = 19.18$ μM) than the one bearing a phenyl substitution. Interestingly, introduction of a nitro group at 3′ position of the phenyl substitution dramatically enhanced the potency as seen in compound **36** ($IC_{50} = 18.91$ μM). However, presence of a nitro group at other positions of the phenyl substitution did not yield promising inhibitors.



36 **37** **38**

Figure 5.10 The 5-arylidene-*N*,*N*′-diethylthiobarbituric acid derivatives. Presence of hydroxyl groups in compound **37** ($IC_{50} = 0.6$ nM) is essential for promising enzyme inhibition.

5.2.6 Carbazoles and hydrazone-bridged thiazole-pyrrole derivatives

Carbazoles and hydrazone-bridged thiazole-pyrrole derivatives have been previously synthesized and reported as antimicrobial agents [16–18]. The compounds are an emerging class of α-glucosidase inhibitors, and the literature has started to witness reports on 1,2,4-triazine-carbazoles [19], 1,2,3-triazole-carbazoles [20], thiosemicarbazines [21], and chromone-hydrazone derivatives [22].

Ghani et al. [23] recently identified carbazoles and hydrazone-bridged thiazole-pyrrole derivatives as α-glucosidase inhibitors that add new structural diversity to α-glucosidase inhibitors discovered to date (Fig. 5.11). The carbazole series of derivatives were identified as noncompetitive inhibitors of yeast α-glucosidase. The most potent inhibitor in the series was **39** containing the 2-benzoimidazole substitution ($K_i = 0.17$ μM) that appears to play a primary role in the enzyme inhibition. A substantial loss of the inhibitory activity was observed when the 2-benzoimidazole group was replaced by a 2-benzothiazole group (**40**; $K_i = 8.25$ μM). The rings of both substitutions differ only by a nitrogen and a sulfur atom, which markedly discriminated their activities. The –NH group of the benzoimidazole moiety is highly selective for

enzyme inhibition apparently due to its participation in forming important hydrogen bonds with the enzyme active site. Compound **41** ($K_i = 11.75\ \mu M$) bearing the 2-benzoxazole ring exerts inhibitory effects similar to that of compound **40**. Moreover, compounds **42** and **43** also exhibited similar levels of inhibition ($K_i = 14.53$ and $14.35\ \mu M$, respectively). In the

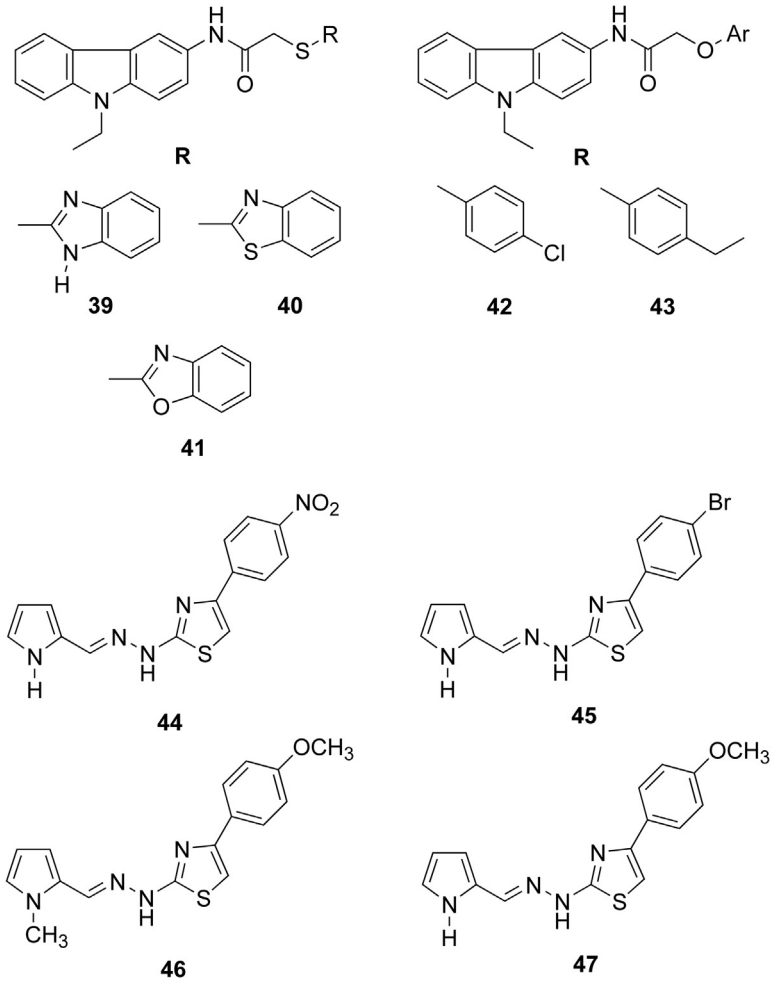


Figure 5.11 The carbazoles (**39**–**43**) and hydrazone-bridged thiazole-pyrrole inhibitors (**44**–**47**) of α-glucosidase offer new structural diversity to antidiabetic drug development.

carbazole series of compounds, the order of potency is based on the type of the substituent ring, that is, imidazole > thiazole > oxazole.

Ghani et al. [23] also studied hydrazone-bridged thiazole-pyrrole derivatives which demonstrated competitive enzyme inhibition. Promising inhibitors in this series include compounds **44** bearing a 4-nitrophenyl group ($K_i = 3.03$ μM), and **45** with a 4-bromophenyl group ($K_i = 3.18$ μM). Both compounds exhibited similar levels of activity despite being different only by a nitro and a bromo group. Moreover, compounds **46** ($K_i = 9.18$ μM) and **47** ($K_i = 6.7$ μM), which are chemically different only by a methyl group on the pyrrole ring, exhibited different levels of potencies. Comparison of their activities showed that the absence of the methyl group in compound **47** is substantially favorable for α-glucosidase inhibition. The carbazoles and hydrazone-bridged thiazole-pyrrole inhibitors of α-glucosidase offer new structural diversity that can be further explored for antidiabetic drug development.

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