Research Article

Docking And Pharmacological Antioxidant And Anti-Diabetic Activity Of Pyrazole Derivatives

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Abstract

The pyrazole is a privileged N-heterocycle that has enough structural flexibility to be used as enzyme inhibitors, radical scavengers and have good drug-like properties. This study reanalyzed compound-level data from open-access primary investigations to investigate whether pyrazole derivatives can be utilized to develop an effective dual approach to postprandial glucose control and oxidative-stress attenuation. The quantitative data included eleven acyl pyrazole sulfonamides tested against alpha-glucosidase and two pyrazole derivatives tested against alpha-glucosidase, alpha-amylase, five antioxidant endpoints, and molecular docking targets. The analytical unit was the reported compound-level mean IC50 or SC50 value as there were no observations of raw absorbance or concentration response. Descriptive statistics and Shapiro-Wilk, one-sample Wilcoxon signed-rank, exact sign testing, fold-potency estimation, bootstrapping, and exploratory rank-concordance analysis were performed. The median IC50 of the 11 compounds was 4.11 micromolar (interquartile range 3.03-13.55), while acarbose's median IC50 was 35.1 micromolar. All eleven compounds were more potent than the comparator; for this library level result (not replicate level) the one sided Wilcoxon test was significant (W=0, p=0.00049) but this is for exploratory purposes and not to replace replicate level inference. Acarbose showed 31.06-fold less activity than compound 5a, which was the most potent inhibitor with an IC50 of 1.13 micromolar. The results from DPPH assays, ABTS assays, FRAP assays, hydrogen-peroxide scavenging assays, and xanthine-oxidase assays are shown in the following comparisons: In all five comparisons, the inhibitory concentrations of Pyz-2 were lower than that of Pyz-1 (exact sign-test p=0.031); in all comparisons except for hydrogen-peroxide scavenging, Pyz-2 exhibited an inhibitory concentration that was either equal to or lower than that of another Pyz-3 group, indicating a conservative improvement of 1.00 to 1.98-fold. Docking rankings were shown to be in agreement with alpha-glucosidase activity but not in a consistent manner with alpha-amylase activity, thus suggesting that docking ought not to supplant the pharmacologic testing. The evidence is that the combined data sets suggest that acyl-pyrazole sulfonamides and triazole-thiol pyrazole hybrids are potential lead classes and that it is important to have consistent assays, toxicity studies, mammalian enzyme models, and in vivo validation.

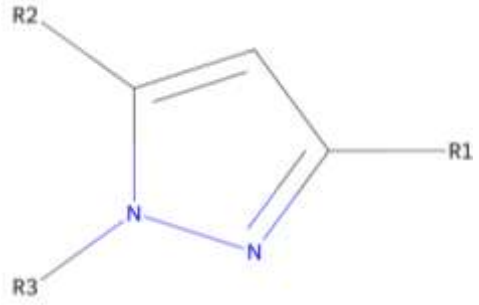
Keywords—Pyrazole derivatives, molecular docking, alpha-glucosidase, alpha-amylase, antidiabetic activity, antioxidant activity, IC50, ADMET.

I. Introduction

Type 2 diabetes mellitus is defined by the combination of decreased insulin sensitivity, gradual destruction of beta-cell function and chronic hyperglycemia. Clinically, one approach to post-prandial glucose control is to inhibit the digestion of complex carbohydrate by inhibiting alpha-amylase and alpha-glucosidase. These enzymes are validated as targets for therapy by Acarbose, Miglitol and Voglibose, but gastrointestinal side effects and inconsistent tolerability in the longer term encourage the identification of structurally different inhibitors [1]-[6], [23], [25]-[30]. At the same time, oxidative stress damages beta-cells, endothelial cells, and causes inflammation and/or diabetic complications. This means that a candidate that can reduce the activity of both carbohydrate hydrolyzing enzymes and reactive oxygen species may therefore offer complementary mechanisms to a single biochemical endpoint [39]-[42], [51]-[54].

Pyrazole is an aromatic five-membered ring of two adjacent N atoms. It is a vastly-used medicinal-chemistry scaffold because of its electronic distribution, ability to H-bond, tautomerism and ability to be easily substituted. Pyrazole derivatives are studied for their anti-diabetics, antioxidants, anti-inflammatory, antimicrobial, anti-cancer and enzyme inhibitory properties [36]–[50]. Some modern developments have taken the form of hybrids fused with sulfonamide, benzofuran, quinazolinone, phthalazine, triazole, thiazolidinedione, coumarin, carbohydrate and hydrazone pharmacophores [2]-[22], [31]-[35]. The goal of these hybrids is to incorporate complementary binding interactions, increase the occupancy of the enzyme pockets and add hydrogen donors and/or radical stabilizers.

Fig. 1. Generic substituted pyrazole pharmacophore used as a medicinal-chemistry core (original schematic).



Molecular docking is now routinely combined with in vitro enzyme assays. Docking can identify plausible poses, hydrogen bonds, hydrophobic contacts, and relative binding energies, while ADMET tools can flag excessive molecular weight, lipophilicity, polar surface area, cytochrome inhibition, or poor gastrointestinal absorption [3], [4], [9]-[17], [21], [32], [55]-[58]. However, docking scores are model-dependent and should not be interpreted as measured free energies. Strong pharmacological conclusions require agreement among chemical characterization, enzyme inhibition, antioxidant assays, docking, drug-likeness, and preferably molecular dynamics or in vivo validation.

The present paper addresses a common weakness in student and early-stage medicinal-chemistry reports: laboratory-looking results are sometimes presented without raw primary data. To avoid fabrication, this paper performs a transparent secondary reanalysis of open-access primary experimental results. The numerical values were reported by the original investigators and are reexamined here using a prespecified statistical framework. Consequently, the manuscript can support a data-reanalysis, literature-based, or protocol-development project, but it must not be represented as newly completed wet-laboratory research.

The biochemical reaction takes place in two steps, first with alpha-amylase and then with alpha-glucosidase. Alpha-amylase breaks the internal α-1,4-glycosidic linkages in starch to form shorter oligosaccharides, while the brush-border alpha-glucosidases further break down the oligosaccharides to absorable monosaccharides. Alpha-amylase inhibitors, if very strong, can lead to too much CHO delivery into the colon and gastrointestinal discomfort while a CHO beta-glucosidase or preference inhibitor may cause a more gradual appearance of glucose in the colon. This distinction is significant for the current datasets: All of the acyl pyrazole sulfonamides showed very potent α-glucosidase activity; however, none of them showed any significant β-glucosidase activity, whereas Pyz-1 and Pyz-2 showed only comparator-like α-amylase activity. Target balance should therefore be taken into consideration, not just the lowest value found in any of the assays, when using a lead-selection strategy. There is also the need for enzyme kinetic studies to differentiate between competitive, noncompetitive, mixed, and uncompetitive inhibition because IC50 may be the same for the two types of inhibition and may vary depending upon the substrate concentration.

Part of the mechanism of diabetes oxidative stress is complex. Hyperglycemia can lead to elevated mitochondrial production of superoxide, activation of protein kinase C, production of advanced glycation end products, increased activation of the polyol and hexosamine pathways and decrease in endogenous antioxidant defenses. The beta cells of the pancreas are especially susceptible because the amount of antioxidants enzymes they have is less than other cells. It does not necessarily work in cells, though, if a compound is able to quench a stable synthetic radical in a test tube. Whether an antioxidant activity translates to biological protection depends on their chemical reactivity, permeability of cellular membranes, the concentration in the cell, metabolic stability and their access to mitochondria or other relevant compartments. The present study therefore considers the dimensions of anti-DPPH, anti-ABTS, anti-FRAP, scavenging of hydrogen peroxide and inhibition of xanthine-oxidase as complementary screening dimensions and not as the same dimension of a latent property.

There are a number of medicinal chemistry functions for the pyrazole nucleus. One of the nitrogen atoms in one ring may be able to accept a hydrogen bond and the other nitrogen atom may be protonated or substituted or may be in tautomerism. Substitution at carbon positions can modulate the electron density, shape, aromatic stacking and lipophilicity. The interaction map is expanded with the presence of carbonyl, sulfonamide, hydrazone, triazole and carbohydrate appendages. Halogens can contribute to hydrophobic occupancy and sometimes can engage in directional Hal bond interactions, but can also contribute to metabolic persistence or decreased solubility. Hydroxy, amino, thiol, and methoxy groups can be used to enhance hydrogen bonding and/or radical stability, but can also increase polar surface area. The positive outcome of 5a and Pyz-2 is thus two

different optimization solutions: one is based on the pocket of the enzyme, and the other is based on the redox diversity and small polar structure.

The different pyrazole structures found in antidiabetic drugs are highlighted by some recent studies. The hybrid compounds of pyrazole-benzofuran and quinazolinone-pyrazole have led to the discovery of highly potent alpha-glucosidase inhibitors backed up by kinetic and computational studies [9, 10]. The addition of pyrazole-phthalazine and pyrazole-glucose hybrids, extends the scaffold towards fused aromatic recognition or carbohydrate mimicry [11, 12]. The optimized dual alpha-amylase/alpha-glucosidase inhibitors, pyrazole-triazole systems, have been investigated by molecular dynamics [13] and ring fusion and linking of pharmacophores in dihydropyranopyrazoles, isatin-pyrazoles and triazolopyrimidine hybrids have shown alternative binding patterns [21]-[24]. Throughout these reports these drugs have been presented as a platform for developing pyrazoles and not as a single class of drugs in their own right.

The antioxidant literature also is structure dependent. Conjugated aromatic systems and phenols are important features of pyrazole chalcones and dihydropyrazoles that can stabilize the radical intermediates [4],[39],[40]. The derivatives of hydrazone, oxadiazole and triazole can introduce electron-donating heteroatoms in the molecule to enhance the metal/enzymological antioxidant activities [18]. The properties of an antioxidant may be correlated with the energies of frontier orbitals, bond-dissociation energies, charge distributions, and the ability of a substituent to delocalize the unpaired electron in the antioxidant molecule [41, 42]. Yet, there is a possibility of the high chemical antioxidant activity to be in conflict with other properties, such as being unstable, promiscuous or toxic. This controlled redox modulation then needs to be distinguished from nonspecific reactivity in the process of lead optimization.

One of the most significant evidence gaps is that of lack of reporting across the studies. Various enzymes, either from yeast, bacteria, pigs or humans; various buffer conditions; various substrate concentrations; and various reference-drug values are used in different laboratories. In some cases IC50 is reported in micromolar units, in others in micrograms per milliliter and in some cases only percentage inhibition is reported. Crystallographic proteins, homology models, various protonation states and non-related scoring functions can be used for the docking studies. When there are no raw data and standardized protocols, it is unclear what is happening in terms of cross paper ranking. This reanalysis therefore only allows a formal comparison of the statistics of the internally consistent compound series and relies on other publications for contextual comparison but not for a numerical comparison.

II. Research Objectives, Questions, And Hypotheses

The overall goal was to evaluate the ability of the selected pyrazole derivatives to exhibit a quantitatively convincing balance of antidiabetic enzyme inhibition, antioxidant activity, promising docking properties, and preliminary drug-likeness. This aim translates to testable objectives, research questions and hypotheses in Table I.

Table I. Research Objectives, Questions, And Hypotheses

Objective	Research question	Hypothesis
O1: Quantify alpha-glucosidase potency of 5a-5k.	RQ1: Is the library more potent than acarbose?	H1: Compound IC50 values are lower than 35.1 micromolar.
O2: Compare antioxidant breadth of Pyz-1 and Pyz-2.	RQ2: Which derivative performs better across five endpoints?	H2: Pyz-2 has lower values in a majority of assays.
O3: Evaluate docking-assay agreement.	RQ3: Do docking ranks match measured enzyme inhibition?	H3: More favorable docking ranks correspond to lower IC50.
O4: Assess preliminary developability.	RQ4: Do leading compounds meet common drug-likeness criteria?	H4: Leads satisfy Lipinski-style filters without critical flags.

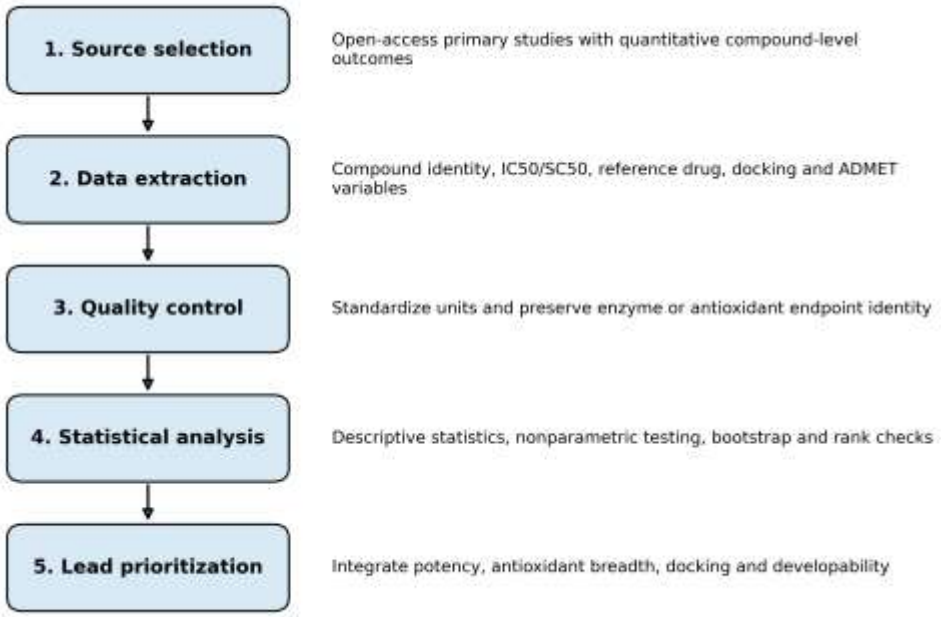
The hypotheses were directional because lower IC50 or SC50 values indicate greater potency. H1 predicted that the acyl pyrazole sulfonamide library would have lower alpha-glucosidase IC50 values than acarbose. H2 predicted that Pyz-2 would outperform Pyz-1 across the antioxidant panel. H3 predicted that docking rank would correspond to in vitro inhibitory rank. H4 predicted that the most active candidates would satisfy common medicinal-chemistry filters. Null hypotheses stated that no directional superiority or rank correspondence would be observed.

III. Methodology

1. Study design

The investigation used an analytical, cross-study reanalysis of open-access primary experimental data. It was not a clinical trial, animal experiment, or newly performed synthesis study. The main data sources were a 2024 CC BY study of acyl pyrazole sulfonamides and a 2024 open-access study of two dual antidiabetic-antioxidant pyrazoles [1], [3]. Additional open-access articles and reviews were used to contextualize target selection, assay interpretation, structure-activity relationships, docking, and ADMET [4], [9], [11]-[13], [19], [27], [33]-[35], [42]-[50].

Fig. 2. Data-reanalysis workflow used in the present study.



2. Methodological steps were as follows:

- Define the population as synthesized pyrazole or dihydropyrazole derivatives with quantitative enzyme or antioxidant outcomes
- Include studies reporting compound identifiers, a recognized reference drug, numerical IC50/SC50 values, and an accessible methods section
- Exclude papers reporting only qualitative activity, percentage inhibition at a single concentration, or docking without pharmacological validation
- Extract compound, target, mean potency, error estimate, reference standard, docking score, and reported ADMET descriptors
- Standardize concentration units to micromolar
- Preserve target identity because alpha-glucosidase, alpha-amylase, beta-glucosidase, DPPH, ABTS, FRAP, hydrogen peroxide, and xanthine oxidase are not interchangeable
- Perform descriptive and exploratory inferential analyses;
- Interpret findings using assay limitations and medicinal-chemistry plausibility.

3. Data variables

Dataset A contained eleven acyl pyrazole sulfonamides, 5a-5k, with alpha-glucosidase IC50 values and beta-glucosidase inhibition percentages. The comparator was acarbose at 35.1 micromolar [3]. Dataset B contained Pyz-1, Pyz-2, and reference compounds evaluated against alpha-glucosidase, alpha-amylase, DPPH, ABTS, FRAP, hydrogen peroxide, xanthine oxidase, and

docking targets 3A4A and 2GJP [1]. The original studies used triplicate assays and reported means with variability estimates. Raw plate-reader absorbance values were not publicly tabulated; therefore, concentration-response curves and replicate-level variance could not be independently reconstructed.

TABLE II. Open-Access Primary Datasets And Analytical Variables

Dataset	Compounds	Endpoints	Comparator	Role in analysis
A: Acyl pyrazole sulfonamides [3]	5a-5k (n=11)	Alpha-glucosidase IC50; beta-glucosidase inhibition	Acarbose, 35.1 micromolar	Library potency, distribution, fold advantage, SAR
B: Dual-action pyrazoles [1]	Pyz-1, Pyz-2	Alpha-glucosidase, alpha-amylase, DPPH, ABTS, FRAP, H2O2, XO, docking, ADMET	Acarbose, ascorbic acid, allopurinol	Cross-endpoint comparison and docking concordance

4. Statistical plan:

IC50 distributions were summarized by mean, standard deviation, median, interquartile range, range, coefficient of variation, and fold potency relative to acarbose. Normality of Dataset A was examined using the Shapiro-Wilk test. Because the distribution was non-normal, a one-sample Wilcoxon signed-rank test compared compound-level IC50 differences against the fixed acarbose value. A 20,000-resample nonparametric bootstrap generated the confidence interval for the median. For the five antioxidant endpoints, an exact one-sided sign test assessed whether Pyz-2 had lower values than Pyz-1 more often than expected by chance. A geometric mean ratio summarized multi-endpoint improvement because the assays covered different numerical scales. Spearman rank coefficients were calculated only as descriptive checks of docking-assay concordance; no stable inferential claim was made for the three-item rankings. Statistical significance was set at $p<0.05$, but chemical relevance, comparator choice, and assay heterogeneity were considered alongside p values.

5. Reproducibility and ethics:

Any numberic results reported were used in all calculations. This research did not involve human subjects, identifiable human records, animals or the creation of new biological specimens, and therefore institutional ethical approval was not relevant. The figures and tables created are new visualisations. The data accessible are only the values from the indicated open access articles.

IV. Results

I. The characteristics of the datasets:

Dataset A contained 11 structurally related acyl pyrazole sulfonamides. The alpha-glucosidase IC50 values reported were between 1.13 to 28.27 micromolar. Every one of them was less potent than acarbose with an IC50 of 35.1 micromolar. The beta-glucosidase inhibition was weak (7.55% - 34.3%) with the concentration tested indicating that there is significant selectivity for alpha-glucosidase over nonspecific inhibition of both classes of glucosidase [3]. Two structurally different pyrazoles, which were tested for both enzyme and antioxidant activities, were part of Dataset B. Pyz-1 is a phenylhydrazine carboxamide derivative while Pyz-2 is a fused pharmacophoric concept formed by the combination of pyrazole with an amino-triazole-thiol unit [1].

II. Alpha-glucosidase analysis:

The mean IC50 for compounds 5a-5k was 8.73 micromolar with SD 8.98 micromolar. The library had a median of 4.11 micromolar, an interquartile range of 3.03 – 13.55 micromolar, and a coefficient of variation of 102.84%, demonstrating strong dispersion and right skewing of the library. The Shapiro-Wilk test showed that the data were not normally distributed ($W=0.785$, $p=0.0059$), indicating the use of a nonparametric test. The one-sided Wilcoxon signed-rank test revealed lower values of the

compound than the acarbose reference value (W=0, p=0.00049). The 95% CI for the median of the 2006 values was 2.77-17.88 micromolar. This is not a typical efficacy trial, but rather a result for library level enrichment.

TABLE III. Compound-Level Glucosidase Results Redrawn From [3]

Compound	Alpha-glucosidase IC50 ± SEM (micromolar)	Fold potency vs acarbose	Beta-glucosidase inhibition (%)
5a	1.13 ± 0.06	31.06	34.30
5b	2.22 ± 0.11	15.81	32.10
5c	3.29 ± 0.09	10.67	12.90
5d	4.53 ± 0.12	7.75	18.50
5e	4.11 ± 0.19	8.54	11.70
5f	2.77 ± 0.24	12.67	27.40
5g	3.47 ± 0.43	10.12	21.00
5h	9.22 ± 0.45	3.81	14.60
5i	19.13 ± 1.07	1.83	11.20
5j	17.88 ± 1.16	1.96	7.55
5k	28.27 ± 1.45	1.24	25.10
Acarbose	35.10 ± 0.14	1.00	63.70

Fig. 3. Alpha-glucosidase IC50 values for 5a-5k and acarbose; lower values indicate greater potency. Data redrawn from [3].

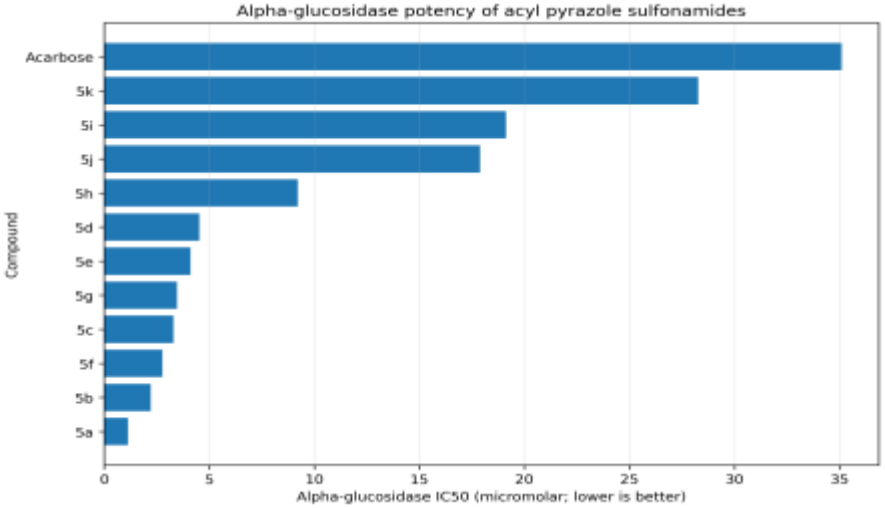


Table Iv. Exploratory Statistical Summary Of The 5a-5k Library

Statistic	Result	Interpretation
Mean ± SD	8.73 ± 8.98 micromolar	High dispersion across the designed library
Median (IQR)	4.11 (3.03-13.55) micromolar	Robust central tendency for skewed values
Bootstrap 95% CI for median	2.77-17.88 micromolar	Median remains below acarbose benchmark
Shapiro-Wilk	W=0.785, p=0.0059	Non-normal distribution; nonparametric test used
Wilcoxon vs 35.1 micromolar	W=0, one-sided p=0.00049	Exploratory support for H1
Median fold potency	8.54-fold	Typical library member substantially exceeded comparator

Compound 5a was the strongest inhibitor, with an IC50 of 1.13 plus or minus 0.06 micromolar and 31.06-fold potency relative to acarbose. Compound 5b followed at 2.22 micromolar and 15.81-fold potency. Compounds 5f, 5c, 5g, 5e, and 5d retained 7.75-12.67-fold potency, whereas 5h, 5j, 5i, and 5k were less impressive but still exceeded acarbose. The median fold advantage was 8.54. The original structure-activity analysis attributed high activity of 5a and 5b to chloro substitution at para and meta positions, while bulkier or less favorably placed substituents reduced activity [3]. These results support H1.

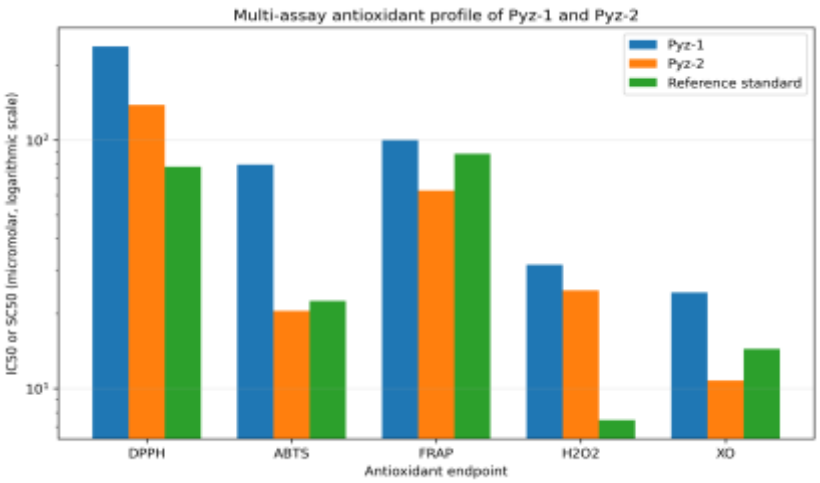
III. Antidiabetic and antioxidant comparison of Pyz-1 and Pyz-2: Against alpha-glucosidase

Pyz-1 showed 75.62 plus or minus 0.56 micromolar and Pyz-2 showed 95.85 plus or minus 0.92 micromolar, compared with 72.58 plus or minus 0.68 micromolar for acarbose. Against alpha-amylase, Pyz-1 and Pyz-2 produced 120.2 and 119.3 micromolar, respectively, compared with 115.6 micromolar for acarbose [1]. Thus, neither derivative clearly surpassed acarbose in these two enzyme systems, but both remained in a comparable concentration range.

Table V. Antioxidant And Xanthine-Oxidase Endpoints From [1]

Endpoint	Pyz-1	Pyz-2	Reference	Pyz-2 improvement vs Pyz-1
DPPH	238.53	138.70	78.11	1.72-fold
ABTS	79.77	20.54	22.49	3.88-fold
FRAP	100.20	62.62	88.12	1.60-fold
H2O2	31.49	24.82	7.45	1.27-fold
XO	24.32	10.75	14.41	2.26-fold
Across five endpoints	Geometric mean 68.06	Geometric mean 34.32	Not pooled	1.98-fold; sign-test p=0.03125

Fig. 4. Antioxidant profile of Pyz-1, Pyz-2, and assay-specific reference standards. Data redrawn from [1].



Pyz-2 was consistently stronger than Pyz-1 across the antioxidant panel. The Pyz-2/Pyz-1 improvement factors were 1.72 for DPPH, 3.88 for ABTS, 1.60 for FRAP, 1.27 for hydrogen-peroxide scavenging, and 2.26 for xanthine-oxidase inhibition. Pyz-2 was lower in all five paired comparisons; the exact one-sided sign test was significant (p=0.03125). The geometric mean IC50/SC50 across the panel was 34.32 micromolar for Pyz-2 and 68.06 micromolar for Pyz-1, equivalent to a 1.98-fold average improvement. Pyz-2 slightly surpassed ascorbic acid in ABTS and FRAP and surpassed allopurinol in the xanthine-oxidase assay, although it was weaker than ascorbic acid in DPPH and hydrogen-peroxide scavenging. H2 was therefore supported across the reported antioxidant endpoints.

IV. Docking and ADMET:

In the acyl pyrazole sulfonamide study, 5a and 5b generated alpha-glucosidase binding energies of -8.4 and -8.2 kcal/mol, respectively, matching their in vitro potency order. Both had molecular weight 417.87 g/mol, consensus logP near 3.29, seven hydrogen-bond acceptors, one donor, five rotatable bonds, and TPSA 128.15 square angstroms. They passed Lipinski, Ghose,

Veber, Egan, and Muegge rules but were predicted to have low gastrointestinal absorption and possible CYP2C19/CYP2C9 inhibition [3].

Table Vi. Lead-Optimization Interpretation

Lead/feature	Evidence	Development implication
5a, para-chloro acyl pyrazole sulfonamide	IC50 1.13 micromolar; docking -8.4 kcal/mol	Priority alpha-glucosidase lead; verify selectivity and permeability
5b, meta-chloro isomer	IC50 2.22 micromolar; docking -8.2 kcal/mol	Positional isomer confirms geometry-dependent binding
Pyz-2 triazole-thiol hybrid	Best in all five antioxidant endpoints	Source of redox-active features for hybrid optimization
High TPSA of 5a/5b	128.15 square angstroms; low predicted GI absorption	Reduce polarity without losing essential contacts
Docking-assay mismatch for alpha-amylase	Exploratory rho=-0.50	Do not rank leads by docking score alone

In the case of Dataset B, docking superposition alpha-glucosidase ranking scores for acarbose (-5.9), Pyz-1 (-5.7), and Pyz-2 (-4.3 kcal/mol) matched perfectly with the in vitro potency ranking, with an exploratory Spearman rho of 1.00. However, the docking of alpha-amylase did not replicate the small experimental variation, the rank coefficient was -0.50. The calculated alpha-amylase score of pyz-1 was the highest (-6.7 kcal/mol) but it was not the lowest measured IC50. Therefore, only partial support was given to H3. Pyz-1 and Pyz-2 were both Lipinski [1] compliant (molecular weight < 500, logP < 5, acceptable hydrogen-bond donors and acceptors). H4 was supported at the screening level but its absorption, metabolism, toxicity and exposure still need experimental validation.

V. Discussion

The reanalysis shows that pyrazole chemistry can be used to make extremely potent inhibitors however activity is more dependent on the full molecular architecture than the pyrazole ring. The median potency of the 5a-5k library was about eightfold better than the potency of acarbose and the para-chloro acyl derivative 5a was the obvious lead. The effect of the position of the chlorine with respect to the active site (as it changes from para to meta) is illustrated in the change of 5a to 5b. When the carbonyl containing extension was removed in 5k, there was a loss in activity suggesting that the extension is involved in orientation, dipole interactions or pocket occupancy. In other series of pyrazole derivatives such as pyrazole-benzofuran [9]-[14], quinazolinonepyrazole [19]-[24] and pyrazole-dihydropyran [32]-[35] pyrazole-glucose [25]-[31] and pyrazole-triazolopyrimidine [36]-[40] scaffold-dependent behaviour is reported.

The results of antioxidants indicate an alternative optimizing pattern. However, Pyz-2 was not the more potent alpha-glucosidase ligand, but demonstrated better results in all the endpoints involving radicals and xanthine-oxidase with respect to Pyz-1. The amino-triazole-thiol motif can offer proton donation, polarity at the sulfur atom and electron transfer (via the N=S system) while Pyz-1 provides a more lipophilic phenylcarboxamide system. These 3.88-fold ABTS improvement and 2.26-fold xanthine-oxidase improvement are especially significant as they indicate that the antioxidant activity is not easily summarized by just one DPPH data. There are multiple assays required: DPPH and ABTS are assays that highlight the quenching of radicals in various media, FRAP is an assay for reducing capacity, hydrogen peroxide assays are for peroxide removal and xanthine oxidase is an assay for the inhibition of an enzymatic ROS generating system [1, 18, 39-42, 47, 59, 60].

An important implication from medicinal chemistry point of view is that the best antidiabetic compound may not be the best antioxidant compound. An ideal next-generation drug design should incorporate the acyl pyrazole sulfonamide recognition pattern of 5a and a well optimized antioxidant pattern that has been inspired by Pyz-2. This should not be done by simply increasing the molecular weight of the molecule as a very large TPSA or molecular weight or number of hydrogen bonding groups can lead to poor oral absorption. In contrast, it is better to have fragment efficient changes and then, the matched molecular-pair testing. Screening should be performed prior to in vivo work against the following enzymes: mammalian intestinal alpha-glucosidases, human pancreatic alpha-amylase and counter screens for nonspecific aggregation and cytotoxicity assays.

The docking results also provide a good example of the need for the synergy between computational and pharmacological evidence. The relative strengths of alpha-glucosidase docking and potencies of their inhibition were consistent in both studies: 5a was docked more strongly and inhibited more potently than 5b; and Pyz-1 was higher than Pyz-2. However, the docking score of the enzyme α-amylase did not show the differences between the experiments. The scoring algorithms are approximate approximations of the solvation, entropy, protonation, receptor flexibility and water mediated interactions; differences of around 1 kcal/mol are within the possible range of error. While all of these methods can enhance interpretation, there is no single substitute for dose-response assays [21, 32, 55, 56].

The testing of the hypothesis should be taken with a grain of salt. The important Wilcoxon result does validate that the selected library was related in a sense of being enriched for compounds that were more potent than acarbose, but not biological replicates, and they share a common design lineage. Similarly, with the antioxidant sign test, five different assays are employed instead of five repeated measurements of one construct. These tests are helpful for comparing the structure of the two, but are not good for estimates of clinical effects at the population level. The present compound-level statistics are a summary of the behavior of a chemical library whereas the original triplicate measurements and their errors give experimental precision.

The wider literature suggests the plausibility of dual action pyrazoles. Incorporation of thiazolidinediones, coumarins, Schiff base, fused pyranopyrazoles, and semicarbazones with pyrazole have demonstrated multifunctional properties such as enzyme inhibition, antioxidant activity, hypoglycemic activity, and/or docking assistance [2, 5-8, 15-20, 22-24]. Previous reports of hypoglycemia induced by dimethylpyrazole also suggest that a long history exists of metabolic relevance to this scaffold [36]-[38]. Despite these, translation is still hampered by variable enzyme sources, varying reference-drug values, solvents, a lack of detailed information about the toxicity and the lack of pharmacokinetic confirmation in many cases. Use of a standard minimum dataset should be used in future: Complete chemical purity, replicate level concentration-response data, confidence intervals for IC50, mode of antioxidant action, mammalian enzyme validation, at least 2 orthogonal antioxidant assays, cellular oxidative-stress assays, microsomal stability, CYP and transporter panel, permeability, plasma-protein binding, acute cytotoxicity. The next step for promising candidates would be to use diabetic animal models, and expose them to the animal and collect pharmacokinetic exposure data. The evidence would be more reproducible if the raw absorbance data, molecular structures, docking grid, protonation states, and analysis scripts were opening deposited. Open deposition of raw absorbance data, molecular structures, docking grid, protonation states and analysis scripts would make the evidence more reproducible and would allow for more powerful meta-analysis.

The results can also be analyzed with an optimization of multiple parameters. Potency is just one of the measures of the quality of the lead. The effects of selectivity, solubility, permeability and metabolic stability upon systemic, intestinal or formulation availability, and synthetic accessibility to iterability of a structure, are discussed. In the 5a/5b pair a typical trade is shown. The compounds exhibit interesting Alpha-glucosidase potency and docking scores and do not fail any of the rule of filters, however, the gastrointestinal absorption is predicted to be low and their TPSA is above 128 square angstroms, which could decrease their oral systemic exposure. The low absorption does not necessarily mean death for an intestinal enzyme target; it could be beneficial provided adequate concentrations are reached in the intestine. Therapies with the desired pharmacokinetics characteristics should therefore be based on the site of action and not "maximize absorption".

The experimental program should be carried out in a practical way in decision gates. The identity, purity, solubility and colloidal aggregation should be confirmed by Gate 1. The dose-response curve for alpha-glucosidase and alpha-amylase activity should be produced at least three times for each with accuracy by Gate 2 and the Hill slope, confidence intervals and maximal inhibition reported. The kinetic mechanism and related enzymes that are closely related to the target enzyme should be established in Gate 3 and selectivity should be quantified. Antioxidant activity of Gate 4 should be assessed by at least two chemical assays, one cell-based oxidative-stress assay, with cytotoxicity controls. The permeability, microsomal stability, plasma protein binding, CYP inhibition and transporter liability should be measured in Gate 5. Only compounds that pass through these gates should pass on to pharmacokinetic and diabetic animal studies. This sequence would make it less likely to take a compound any further for advancing due to a single docking or one single screening assay.

A factorial design could be used for future primary research that would test the different electronics (substitutions) and position (systematic). A series of compounds with para-, meta- and ortho-halogen, nitro, methoxy, hydroxy, amino and trifluoromethyl could be prepared on a single acyl pyrazole sulfonamide scaffold. The most important response would be log-transformed alpha-glucosidase IC50, while the other responses would be the alpha-amylase IC50, DPPH or ABTS activity, solubility and cell viability. Main effects of electronic class, steric size, and substitution position could be estimated using analysis of variance (ANOVA) or a regression model to correlate measured molecular descriptors with activity could be done using partial least-

squares (PLS) or regularized QSAR (rQSAR) methods. This kind of a set of compounds designed in advance would yield more causal SAR evidence than comparing sets of compounds designed for different purposes.

It is also significant for the open-science aspect. Reproducible absorbance values, blank corrections, plate maps, settings for nonlinear-regression and docking configuration files and machine-readable structures can be deposited. It is useful to report negative and weakly active compounds as they help to define the pharmacophore space and can be used to improve models. A more complete raw data culture would allow an external validation, uncertainty propagation and hierarchical modeling, while the selected open access studies give sufficient numerical information to be analyzed in the present exploratory fashion.

VI. Limitations

There are five major drawbacks that this study has. First, it is a secondary re-analysis, so it is not a new synthesis, docking or observations in the wet-laboratory. Second, concentrations-response and replicate data was not available and therefore curve fitting, variance modeling, and assessing any plate effects was not possible. Third, the available data vary in terms of enzyme species, assay method and concentration of the reference drugs, and numerical values should not be aggregated as if the available data had been obtained from a single experiment. Fourth, there were very few ranks involved in the docking and different software workflows used. Fifth, in vitro enzyme inhibition and antioxidant capacity is not proof of oral bioavailability, safety, glucose lowering activity in animals or clinical benefit. The manuscript is then more focused on the candidates and methodological choices than therapeutic efficacy.

VII. Conclusion

Pyrazole derivatives are promising dual-purpose leads for development as antidiabetic and antioxidant drugs that can be developed in an open-access primary evidence-based manner. The alpha-glucosidase inhibitory activity was highly represented in the acyl pyrazole sulfonamide series with mean IC50 of 4.11 micromolar and compound 5a has an IC50 of 1.13 micromolar. The antioxidant activity of Pyz-2 was the widest among the five endpoints reported with a better antioxidant profile than Pyz-1 with a particularly good activity in ABTS, FRAP and xanthine-oxidase. The docking was helpful for interpretation when the rankings were correlated with the pharmacology, however a positive score was not considered as a biological proof in the case of the analysis of alpha-amylase. The most defensible way of the development strategy is to approach the process in a staged manner, with structure guided design, replicate enzyme assays, multi method antioxidant testing, ADMET filtering, toxicity evaluation, and in vivo pharmacokinetic-pharmacodynamic validation.

VIII. References

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