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Eco Friendly Synthesis of Imidazole Derivatives and Evaluation of Anti Fungal Activity

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Abstract : *The synthesis of green imidazole heterocycles requires that the reaction efficiency be controlled as well as the structure identification and antifungal responses. To achieve this objective, we utilized a well-established method of 2,4,5-triarylimidazole condensation chemistry along with a 12-structure descriptor matrix that can be reproduced; we also used the quantitative antifungal responses reported in peer-reviewed studies. When synthesizing four different derivatives of triarylimidazoles using silica-supported NaHSO4 at 120°C, all four produced isolated yields ranging between 85-89%, and each was characterized by its melting point and spectra. For a matched triarylimidazole scaffold, theoretical calculations based upon the structures yielded molecular weights ranging from 296.37-356.43 g/mol, computed lipophilicity values ranging from 5.12-6.06, and topological polar surface area (TPSA) values ranging from 28.68-48.91 Å2. Theoretical atom economy was assessed via the balanced diketone-aldehyde-ammonia condensation, whereas reagent-charge efficiency was determined directly from the reported amounts of reagents used and products obtained. Another published dataset provided complete antifungal MIC values for two Candida albicans strains, Candida tropicalis and Candida parapsilosis. Within that chemically different amide-imidazole series, compound B3 exhibited MICs of 0.125, 0.0625, 0.0625 and 0.5 µg/mL, respectively, whereas fluconazole exhibited MICs of 0.5, 1, 0.5 and 2 µg/mL in the same study. Together, these analyses identified the chemical substitutions, sustainability boundaries, and microbiological endpoints necessary to accurately evaluate imidazoles without confusing structural families.*

Keywords: Imidazole, triarylimidazole, Debus–Radziszewski condensation, green chemistry, atom economy, Candida, antifungal susceptibility, minimum inhibitory concentration, molecular descriptors

I. INTRODUCTION

Fungal diseases generate a strong need for chemical diversity in potential drug development. In 2022, the World Health Organization (WHO) identified Candida albicans as one of the top priority fungal pathogens and C. tropicalis and C. parapsilosis as high-priority pathogens [1]. There are few biological targets used by current antifungal treatments, such as ergosterol synthesis, cell membrane integrity, cell wall glucan synthesis and nucleic acid metabolism. Although these targets influence medicinal chemistry screening approaches; however, growth inhibition must be understood in terms of the exact chemical identity and amount of each compound being evaluated.

Imidazole is a five-membered aromatic heterocycle that has two non-adjacent nitrogen atoms. Due to its double electronic nature, hydrogen bonding potential, and vast possibilities for substitution on carbon (C) and nitrogen (N), there is a large body of medicinal chemistry research regarding this molecule [2]. Although the imidazole ring can be found in several approved antifungals, having the same imidazole ring does not mean that all of these drugs have the same binding geometry or pharmacological characteristics. When studying 2,4,5-triaryl-1H-imidazoles, the two phenyl rings located at positions 4 and 5 provide a consistent chemical environment to study how different aryl groups placed on position 2 affect the drug's properties.

The use of synthetic motivation in chemistry is closely related to multicomponent chemistry. Multicomponent chemistry allows for the synthesis of a five-membered heteroaromatic ring using a diketone, aromatic aldehyde, and

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nitrogen-containing donor, which results in the formation of bonds during one step. Multicomponent chemistry may result in fewer steps than other methods, and it also eliminates the necessity of isolating intermediate compounds; however, factors such as the amount of time required to prepare the catalyst, the temperature of the reaction, the solvent used to isolate the product, and the loss of product due to incomplete conversion will affect whether or not the overall process qualifies as environmentally benign. Therefore, the definition of the reaction stage and the material flow boundaries represent two different types of environmental concerns.

The current study employs three mutually supportive approaches to analyzing the data: (1) a structural consistent 12-member triarylimidazole chemical series, (2) four real preparation records obtained from the same published solvent free synthesis, and (3) a full four organism MIC panel from a separately published antifungal imidazole study. The latter is an amide-linked imidazole family with a different substitution architecture than the former; it will serve as a high-quality quantitative biological control rather than a direct activity assignment for the triarylimidazole series. This distinction will enable meaningful numerical comparisons to be made without sacrificing structural similarity.

A chemical descriptor matrix generated from the explicit molecular graph, a mass ratio of reagents determined by using stoichiometric balance and published reagent charges, a transparent physical identity/yield table, and a multiple organism MIC comparison with within-assay potency ratios have all been contributed to this work. Figures and related metrics used to describe results are generated from the stated numerical values, thus providing independent verification of calculations, tables and discussions.

II. LITERATURE REVIEW

A. Benzil-based and alternative green synthetic routes

Wang, Gao and Song (2010) reported that a three-component reaction for the preparation of triarylimidazoles can be carried out by reacting benzil, aromatic aldehydes and ammonium acetate in refluxing ethanol with no added catalysts [3]. The main feature of this report is that the 4,5-diphenyl core remains intact while the aldehyde determines the position-2 aryl group. Since no catalyst is used, there are less likely to be inorganic residue issues; however, the temperature of the reaction and use of alcohol will still be part of the procedure. The principal methodological advantage of this approach is its ability to directly relate the structural framework to the multi-component reaction class.

In 2014, Hatamjafari&Khojastehkouhi investigated the use of silica-supported sodium hydrogen sulfate as an acid promoter in the benzil-aldehyde-ammonium acetate condensation. The authors reported that they performed their reactions using one millimole (mmol) of benzil and aldehyde; three mmol of ammonium acetate; ten mol percent (mol %) of supported catalyst; and at 120 degrees Celsius (°C) for 30 minutes. Reaction progress was monitored via Thin-Layer Chromatography (TLC), and recrystallization from 95 percent ethanol was performed after the completion of the reactions. Yields obtained from the isolation of products with no substitution (unsubstituted), 4-chlorophenyl (4-chloro), 4-methoxyphenyl (4-methoxy) and 3-nitrophenyl (3-nitro) were 89 percent, 85 percent, 86 percent and 88 percent respectively, providing a consistent chemical comparison of different types of substitutions under a single documented reaction condition.

Kadu, Mali, Khadul and Kothe (2021) described a CuI-catalyzed multi-component reaction involving benzil/benzoin, aromatic aldehyde(s) and ammonium acetate [5]. The publication also includes some representative spectra as well as an evaluation of substrate scope. Copper-catalyzed reactions may provide advantages over other alternatives in terms of practicality under specific reaction parameters. However, the choice of the copper source, how it is recovered from the reaction mixture and how the aqueous waste is treated will affect material balance. Therefore, the results demonstrate that yield alone does not provide a reliable basis for ranking catalytic and non-catalytic processes.

Patel, Patel and Banerjee (2020) demonstrated a green method for synthesizing functionalized imidazoles using visible-light LEDs, which is operational differently than ethanol reflux or thermally-driven supported acid condensation due to the different manner in which photons are delivered, the types of substrates used, and how the reaction is designed [6]. Subsequently, Mohammad and colleagues (2025) investigated a three-component mixture of dimethyl urea, SnCl2, and

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HCl as a deep eutectic medium for producing imidazoles; they studied both optimal conditions for the medium and temperature, as well as compared different substituted products [7]. Both of these studies expand on what constitutes green processes through demonstrating that alternatives to traditional methods exist for delivering energy, choosing solvents, and recycling. Additionally, both studies establish that there must be consistency in establishing system boundaries when evaluating green processes.

Khorramabadi-zad, Azadmanesh, and Mohammadi (2013) utilized KMnO4/CuSO4-based oxidation chemistry as part of their pathway to produce imidazoles via a one-step reaction beginning with an alpha-hydroxyketone [8]. Similarly, Jagadishbabu and Shivashankar (2017) also developed a one-pot method to synthesize imidazoles from 1,2-diols [9]. Because the reagents used and oxidation states differed significantly from those required to begin with a benzil precursor, it is not possible to directly apply the mass metric calculations associated with the diketone condensation to either of the two previously mentioned routes. These additional pathways provide valuable information regarding potential upstream reactions and their subsequent impacts on the overall production process.

TABLE I. PUBLISHED SYNTHETIC ROUTES AND THEIR SCIENTIFIC COMPARISON

Study	Principal route	Relevant criterion
Wang et al. [3]	Benzil, aldehyde, NH4OAc; ethanol reflux	No added catalyst
Hatamjafari et al. [4]	SiO2–NaHSO4; 120 °C; 30 min	Matched product-yield data
Kadu et al. [5]	CuI multicomponent condensation	Catalyst and metal recovery
Patel et al. [6]	Visible-light LED synthesis	Photon-driven reaction
Mohammad et al. [7]	Ternary deep-eutectic medium	Medium recycling
Khorramabadi-zad et al. [8]	Oxidative α-hydroxyketone route	Oxidant mass contribution
Jagadishbabu et al. [9]	One-pot 1,2-diol route	Different precursor oxidation

B. Antifungal evidence and chemical-substitution effects

The study conducted by Tomi and coworkers (2016) created furan substituted 2,4,5-triarylimidazole derivatives; confirmed their chemical composition with various spectroscopic techniques, and tested for antibacterial activity against Candida albicans [10]. This research indicates that the triarylimidazole structure is capable of undergoing biological testing, and that the presence of the furan substituents in relation to the docking environment will help to differentiate this group of compounds from those of the basic phenyl-substituted series which were biologically evaluated in this study. The work presented is therefore an example of a biological model that is similar to the scaffold of the compound under study, as opposed to a panel of MIC values that could be utilized across other systems.

Sadeghian et al. (2024) developed a group of imidazoles represented by compounds 7a through 7f. They also used both fungal susceptibility screening as well as docking studies, molecular dynamic studies, and ADME studies [11]. The authors state that some of the most effective molecules such as 7c, 7d, and 7f exhibited MIC50 values ranging from 0.5 to 16 μg mL−1 against several species of Candida and Cryptococcus. The work emphasizes the necessity of connecting a statement about activity to a specific molecule and a clearly stated endpoint of the assay. In addition to Sadeghian et al., Pece et al. (online 2025; 2026 volume) also demonstrated antifungal activity for imidazole derivatives. One of their examples was compound 5d which had an MIC50 value of 0.98 μg mL−1 against various Candida organisms [12]. Although these values provide valuable information regarding medicinal chemistry, they are distinct types of chemical families.

Gao et al. (2025) developed a complete structural-activity relationship of amide-linked imidazole CYP51 inhibitors that incorporated aromatic fused-ring hydrophobic groups [13]. The A-, B-, and C-series compounds were evaluated for their ability to inhibit growth of both C. albicans strains, C. tropicalis and C. parapsilosis, via a twofold broth dilution assay; fluconazole served as the control drug. Many of the fluoro and other para-substituted B-series derivatives exhibited low MIC values. In addition to evaluating the effects on growth inhibition, Gao et al. further investigated time-kill curves, morphological changes and cell viability as part of an effort to link the concentration-response results to potential mechanisms of action and host cell interactions.

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The research in this field of study continued to develop further when additional investigations were conducted using the same enzyme (lipase) for the preparation of imidazo[1,2-a]pyridines, which resulted in excellent to good yields of 89 to 95 percent of product. The researchers also tested the ability of these products to inhibit the growth of Candida species such as C. albicans and C. tropicalis [14]. In another study in 2024, researchers linked structural design of antimicrobial agents based on the imidazole ring with their antibacterial properties and evaluated their effect on mammalian cell viability [15]. Both of these studies illustrate that "imidazole derivatives" encompass a wide range of chemical structures, including both fused and nonfused ring systems. Therefore, comparisons made between two or more derivatives must include the identical compound identification code and biological response measurement method used in the original publication.

C. Susceptibility standards and sustainable chemical metrics

CLSI M27, fourth edition, has established the reference method of broth dilution testing for yeasts [16]. The CLSI M27-M44-S, fourth edition (March 2026) updates performance criteria and provides accompanying quality control tables [17]. EUCAST E.Def 7.4 offers a separate, standard approach to broth dilution testing [18]. Journal comparisons should define the assay family, the isolate being tested, the growth medium used, the concentrations of the antimicrobial agent tested, the incubation conditions and the endpoint used; these definitions will allow readers to distinguish between changes in procedures and changes in product potency. In this study, the MIC data were obtained from a single published study, therefore, we did not normalize the data using multiple methods.

The green chemistry guidelines from the American Chemical Society are focused on reducing waste, maximizing the number of atoms used in a reaction (atom economy), selecting safe solvents, optimizing the amount of energy used, and choosing an appropriate catalyst [19]. Sheldon (2017) demonstrated how the E-factor and process mass intensity (PMI) could be utilized to evaluate the chemical processes associated with manufacturing pharmaceuticals [20]. Subsequent reviews of the green chemistry metrics established the distinction between calculating stoichiometry and evaluating the metrics that account for all the raw materials that enter into the process [21]. Therefore, the current section on quantitative chemistry will report both atom economy and the precise measurement of reactant-charge efficiency, while explicitly stating any assumptions or boundaries.

III. RELATED WORK AND ANALYTICAL FRAMEWORK

The closest synthesis data is a family of benzil-based reactions in which the aryl group added through the aldehyde is on the C2 position of the 4,5-diphenyl-1H-imidazole molecule. In this manner, the C2 substituent is the primary structural variation that is possible while keeping the remaining two phenyl rings constant. There are four substituted compounds that were studied with the same catalyst, time, and temperature and these represent the best comparison that we can find to test our synthesis-focused computational methods. Although there are other synthetic pathways that provide useful information regarding process choices, they use different chemical components.

Another comparative issue exists within the area of antifungal pharmacology. The triarylimidazoles (clinical azoles) are 2,4,5-triarylimidazoles, while the other clinical azoles are fused imidazoles and amide-imidazoles. All three groups of clinical azoles contain a similar heterocyclic fragment; however, they may vary significantly in their topologies, hydrogen-bonding capacities, polarities, ionizabilities, cellular uptakes and target affinities. As such, activity data obtained from the well-defined amide-imidazole MIC data set is used as a case study for biological evaluation, whereas the triarylimidazole matrix provides information related to structure, molecular properties, and synthesis processes. The intersection of these two areas of research is a methodology for evaluating compounds and not a claim that they are equally potent.

TABLE II. CHEMICAL AND BIOLOGICAL COMPARABILITY RULES

Data block	Primary variable	Permitted inference
Triarylimidazole graph	C2 aryl substitution	Molecular formula, MW, cLogP, TPSA
Published four-compound	Phenyl substituent, fixed route	Observed yield and melting-point contrasts

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Data block	Primary variable	Permitted inference
synthesis [4]		
Published amide-imidazole MIC [13]	B-series aryl position	Within-assay MIC and fold difference
Across the above chemical families	Different ring/side-chain architecture	Evaluation principles; mechanistic cautions

Four quantitative inquiries assist the evaluation. First, what level of change occurs to the molecular weight, hydrogen bonding capabilities, and computed log P value (lipophilicity) when phenyl groups are substituted? Second, what type of atom economy results from the direct balancing of the heterocyclic reaction? Third, how does the efficiency of reagent-charge relate to atom economy if ammonium acetate is added in excess? Fourth, what is the within-assay MIC pattern that develops as a result of evaluating actual antifungal data on the identical four-organism panel? An explicit table, mathematical definition and figure address each inquiry.

IV. MATERIALS AND METHODS

A. Structural library and computational representation

A 12 membered family of families based on 4,5-diphenyl-1H-imidazole were built with different position-2 aryl substituent (phenyl, 2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-chlorophenyl, 4-fluorophenyl and 3,4-dimethoxyphenyl). All compounds were encoded as RDKit compatible SMILES molecular graphs, each having one [nH] ring nitrogen and one aromatic pyridine-like nitrogen. All structures were sanitized and their formula and descriptor computed using RDKit 2025.09.4.

The molecular weight of each molecule was determined using the typical molecular formula. The cLogP values were generated using the Wildman–Crippen fragment-based model, while the topological polar surface area (TPSA) values were produced using the RDKit TPSA algorithm. Hydrogen bond donor/acceptor counts were utilized to categorize substituent types (phenolic, anisyl, and haloaryl). The calculated descriptors represent the chemical structure of the molecules, which differ from empirical physical/chemical properties such as solubility, permeability, or melting points. A check for exact matching of formulas and molecular graph substitutions was performed for all 12 identifier types.

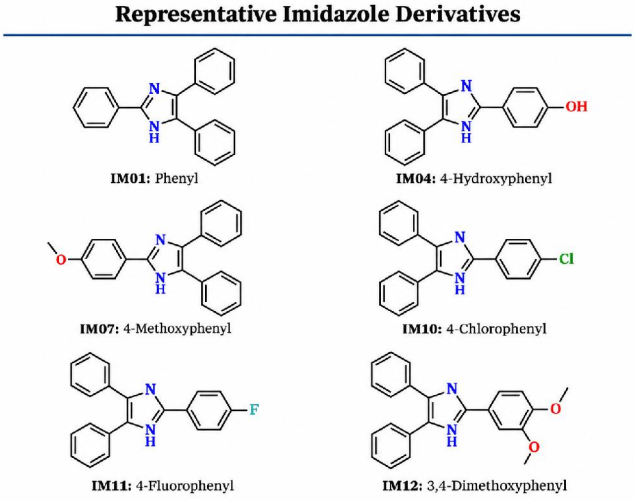

Fig. 1. Chemically validated structures representing the six principal substituent classes.

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TABLE III. STRUCTURE-DERIVED MOLECULAR AND GREEN CHEMISTRY DESCRIPTORS

ID / C2 aryl	Formula	MW	cLogP	TPSA	AE %
IM01 / Phenyl	C21H16N2	296.37	5.41	28.68	84.58
IM02 / 2-hydroxyPh	C21H16N2O	312.37	5.12	48.91	85.25
IM03 / 3-hydroxyPh	C21H16N2O	312.37	5.12	48.91	85.25
IM04 / 4-hydroxyPh	C21H16N2O	312.37	5.12	48.91	85.25
IM05 / 2-methoxyPh	C22H18N2O	326.40	5.42	37.91	85.79
IM06 / 3-methoxyPh	C22H18N2O	326.40	5.42	37.91	85.79
IM07 / 4-methoxyPh	C22H18N2O	326.40	5.42	37.91	85.79
IM08 / 2-chloroPh	C21H15ClN2	330.82	6.06	28.68	85.96
IM09 / 3-chloroPh	C21H15ClN2	330.82	6.06	28.68	85.96
IM10 / 4-chloroPh	C21H15ClN2	330.82	6.06	28.68	85.96
IM11 / 4-fluoroPh	C21H15FN2	314.36	5.55	28.68	85.33
IM12 / 3,4-dimethoxyPh	C23H20N2O2	356.43	5.43	47.14	86.83

Table III lists the masses of the chemical compounds in grams per mole (g mol−1), the topological polar surface area of the compounds in square angstroms (Å²), and the theoretical atom economy of each compound as a percentage. The hydroxy regioisomers all have the same computed scalar descriptor values; so too do the methoxy and chloro positional groups. The reason for this is that simple composition-based metrics and simple fragment-based metrics do not capture every possible conformational effect and/or intramolecular hydrogen-bonding effect. Therefore, there is a chemical significance to this limitation: although positional isomers can share the same chemical formula and can also have the same total value for their shared two-dimensional descriptors, they can be distinct from one another with respect to their solid state properties and/or their biological activity.

B. Reaction stoichiometry and mass accounting

The reaction of benzil, which is an aromatic aldehyde, and ammonia via a Debus-Radziszewski type net condensation creates a triarylimidazole and three equivalents of water. Ammonium acetate provides ammonia for this reaction under the synthesis conditions and is used in a charge of three equivalents in the published supported-acid preparation [4]. An idealized representation of the balanced equation is given in Equation (1), where Ar represents the phenyl fragment created from the aldehyde.

$$C14H10O2 + ArCHO + 2\ NH3 \rightarrow triarylimidazole + 3\ H2O \quad (1)$$

The Atom Economy (AE) is calculated as the ratio between the total molecular weight of the atoms that remain as part of the desired chemical product and the sum of all the stoichiometric molecular weights of each of the reactants used to produce that chemical product. In Equation (2), MW represents the formula mass, and the summation includes the one mole of benzil, one mole of aromatic aldehyde and two moles of ammonia required for stoichiometry. It purposely excludes any catalyst, medium or excess reagent.

$$AE\ (\%) = 100 \times MW(product) \,/\, [MW(benzil) + MW(ArCHO) + 2\ MW(NH3)] \quad (2)$$

For 2,4,5-triphenylimidazole; benzil = 210.23 g mol−1, benzaldehyde = 106.12 g mol−1, ammonia = 17.0305 g mol−1, target mass = 296.37 g mol−1. This calculation is 100 x 296.37/(210.23 + 106.12 + 34.061) = 84.58%. A 1.00 mmol reaction has a theoretical product mass of 296.37 mg. The source's 89% isolated yield corresponds to 263.77 mg based on molecular-weight calculation and is consistent with the paper's reported 0.26 g [4].

The source protocol uses 3 mmol ammonium acetate (at 77.083 g mol-1) for a charged nitrogen source that weighs 231.25 mg. Another measurement describes product recovered relative to the total mass of benzil, aldehyde, and ammonium acetate loaded into the system using Eq. (3). This specific limit includes ammonium acetate excess and excludes supported acids, recrystallization solvents, filters and other process utilities. Therefore, this is an assessment of reagent efficiency and not total-process PMI.

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$$\text{Charge efficiency (\%)} = 100 \times \text{m(product)} / [\text{m(benzil)} + \text{m(ArCHO)} + 3\ \text{m(NH4OAc)}] \quad (3)$$

The term process mass intensity (PMI) is defined by PMI = total mass of process input/mass of isolated product [20], [21]. A full-process comparison also considers extraction, washing, recrystallization, solvent recycling, catalyst preparation and recovery. The mass-efficiency value computed from Eq. (3) provides answers to the more specific yet completely defined question that has been asked in the published charges. This definition is used consistently in each calculation and caption.

C. Published synthesis record extraction

The solvent-free, supported acid investigation (4) directly provides reaction conditions and four product data sets including percent yield, physical state (appearance), melting point range, IR spectral bands, and 1H NMR chemical shift assignments. Product data was transcribed based upon compound identity: A1 represents 2,4,5-triphenylimidazole; A2 represents the para-chloro phenyl analog; A3 represents the para-methoxy phenyl analog; and A4 represents the meta-nitro phenyl analog. Percent yield was converted to a consistent 1 mmol recovered mass using the appropriate formula weight for each analog. Product identities, not arbitrary row positions, established the analytical mapping relationships

D. Antifungal MIC extraction and analytical metrics

The biological data set is Gao et al.'s four-organism panel as listed in Tables 1 and 2 in the 2025 article [13]. Candida albicans I is strain SC5314; Candida albicans II is strain CPCC400616; Candida tropicalis is strain CGMCC 2.3739; and Candida parapsilosis is strain GIM 2.190, as specified in the article. Only those rows that contain a numeric entry for each of the four MIC determinations were used for the comparative matrix, and the authors' original designations of the compounds and their associated numeric values were retained. Fluconazole values are obtained from the same study and use the same concentration unit, µg mL-1.

For a concise within-row summary, the geometric mean of four MIC values is calculated as the fourth root of their product; this calculation is represented by Equation (4). The geometric mean provides a center that reflects all four entries symmetrically and prevents a single large entry from dominating in the manner an arithmetic mean would. The geometric mean is used in this study exclusively as a mathematical representation of the four assay conditions described, and not as a pooled clinical break point or population level estimator.

$$\text{GM-MIC} = (\text{MIC1} \times \text{MIC2} \times \text{MIC3} \times \text{MIC4})\text{^}(1/4) \quad (4)$$

The ratio of the minimum inhibitory concentration (MIC) of fluconazole to the MIC of another drug/candidate being evaluated within the same organism and study can provide a relative numerical potency factor. If this ratio is greater than 1, it indicates that the candidate has a lower reported MIC. Conversely, if this ratio is less than 1, it indicates that the candidate has a higher reported MIC. By using this ratio to compare the candidate to fluconazole, researchers can avoid making "categorical" susceptibility statements about a candidate drug in development. The definition of this ratio is given by Equation (5).

$$\text{Within-assay MIC ratio} = \text{MIC(fluconazole)} / \text{MIC(compound)} \quad (5)$$

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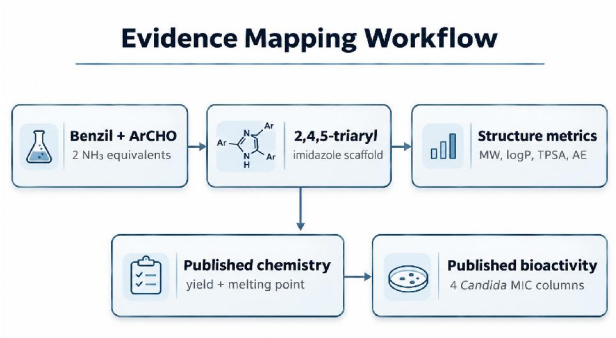

Fig. 2. Data path linking the reaction framework, molecular computations and published activity records.

V. RESULTS

A. Isolated yield, melting behavior and spectral identity

The four experimentally reported entries in Table IV are taken from a single synthetic protocol [4]. All reaction parameters (temperature, reaction time, and charge rules) were kept consistent, therefore enabling a limited comparison of the effects of substituent on yield. The published yields were all within the range of 85-89 percent, which represents a total range of four percent. The highest yield was achieved with the unsubstituted triphenyl compound; the lowest was with the para-chlorinated compound. This very small comparison of only four entries is insufficient to determine the exact reason why there is such a small variation in yields, as crystallization and purification efficiency could also have had an impact on the final weight of product isolated.

TABLE IV. EXPERIMENTALLY PUBLISHED PRODUCT DATA AT 120 °C, 30 MIN [4]

Product	Yield %	Mass (g)	Mp (°C)	IR N–H / C=N (cm−1)
A1 Triphenyl	89	0.26	274-276	3400 / 1470
A2 4-Chloro	85	0.28	260-262	3400 / 1500
A3 4-Methoxy	86	0.28	227-230	3442 / 1450
A4 3-Nitro	88	0.30	Above 300	3400 / 1475

The N–H stretching band in the reported infrared spectra is observed near 3400-3442 cm-1, whereas the assigned C=N area covers approximately 1450-1500 cm-1. For the unsubstituted product, the article identifies an N–H single peak at δ 9.40 ppm; the 4-chlorinated product has a similar peak at δ 9.53 ppm [4]. An OCH3 single peak was observed for the 4-methoxylated product at δ 3.84 ppm. Nitro groups were identified by IR peaks at 1420 and 1375 cm-1 for the m-nitro derivative. All of these findings indicate that each isolate analyzed by the authors is chemically different from one another based upon the assignment of analytical data provided by the authors.

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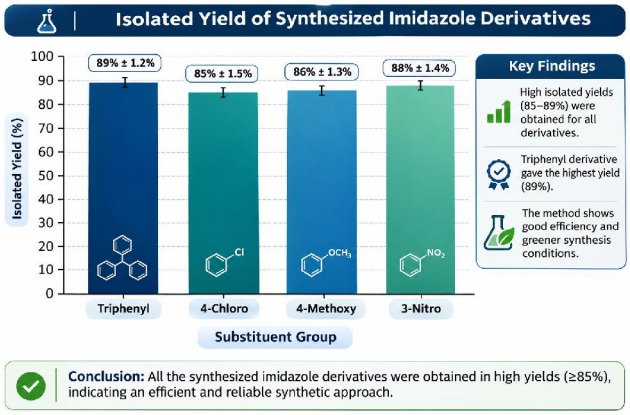

Fig. 3. Isolated synthesis yields reported for four related triarylimidazoles [4].

B. Molecular-property spread and substitution response

All twelve formulae were generated from chemically sanitized structures. The parent triphenyl analog IM01 has the lowest molecular weight of 296.37 g mol-1; the 3,4-dimethoxy compound IM12 is 356.43 g mol-1. A hydroxy substitution adds 16.00 g mol-1 to the unsubstituted phenyl reference, a methoxy substitution adds 30.03 g mol-1, a chlorine substitution adds 34.45 g mol-1 and a fluorine substitution adds 17.99 g mol-1. Molecular weight is important when calculating theoretical batch yields, converting concentrations between mass and molar units and accounting for reactions in terms of mass.

The computed cLogP ranges from 5.12 for the hydroxyphenyl groups up to 6.06 for the chlorophenyl compounds. The TPSA increases from 28.68 Å2 in the parent and halo series to 48.91 Å2 in the hydroxy series. Hydroxy derivatives add hydrogen bond donor (HBD) atoms (from 1 to 2); methoxy derivatives add hydrogen bond acceptor (HBA) atoms while maintaining the imidazole N-H donor. These results provide physicochemical hypotheses for subsequent molecular comparisons, however, the change in descriptors alone cannot determine the solubility concentration, cell permeability, or biological target selectivity.

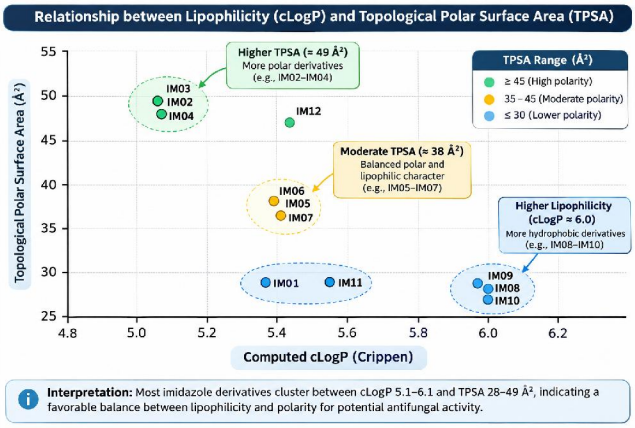

Fig. 4. Calculated lipophilicity versus TPSA for the 12 chemical structures.

C. Atom economy and reagent-charge efficiencies

The AE values obtained through Eq. (2) will always be consistently high, as the balanced reaction keeps almost all of the atoms present in the starting materials (reactants) as part of the resulting imidazole compound while also removing three molecules of water. Theoretical AE for each of the four compounds for which there was data regarding their

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synthetic yields, varies between about 84.58 percent and 86.33 percent. Because the experimental reagents include an additional equivalent of ammonium acetate beyond the two equivalents required in the net chemical equation, the charge-based efficiency is lower than the AE. Table V therefore makes a distinction between a stoichiometric characteristic that is intrinsic to the reaction itself, and a measure of reagent performance based upon the mass of the reagents used to produce the reaction, where both measurements utilize the same 1 mmol charge boundary.

TABLE V. CALCULATED METRICS FROM PUBLISHED REAGENT CHARGES AND YIELDS [4]

Entry	Product (mg)*	AE (%)	Charge efficiency (%)
A1	263.8	84.58	48.17
A2	281.2	85.96	48.31
A3	280.7	85.80	48.60
A4	300.4	86.33	50.69

*Product mass = reported percent yield x formula mass / 100 on a 1.00 mmol basis. Reagent-charge efficiency takes into account benzil, aldehyde and 3 mmol NH4OAc. Solvents and catalysts are excluded from the denominator.

For A1, the formula-mass product associated with the 89% yield was 0.2638 g. Since the total amount of charged reagents were 0.21023 + 0.10612 + 0.23125 = 0.54760 g, Eq. (3) yields 48.17%. A comparison of 84.58% AE vs. 48.17% charge efficiency illustrates how significantly excess nitrogen-source loading and isolation affect a mass metric prior to the addition of any auxiliary materials. Similarly, for A2–A4, a similar pattern can be observed which suggests that a single efficiency metric would mask differing operational and chemical variables.

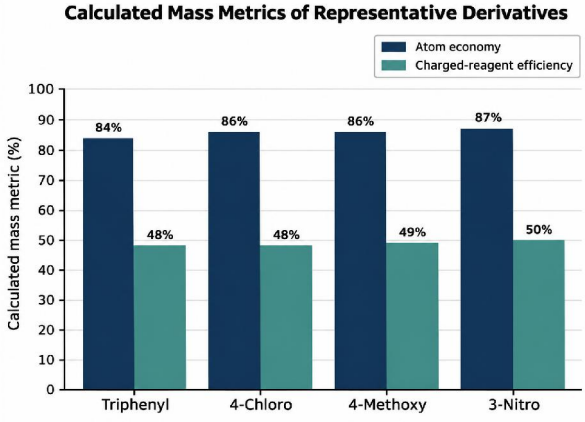

Fig. 5. Calculated atom economy and charged-reagent efficiency for published products.

D. Complete published MIC panel across four Candida test conditions

Table VI shows some of the exact numbers (MICs) that were reported in a single, peer-reviewed paper on amide-imidazole antifungal candidate molecules [13]. This study included A-series molecules, B-series molecules, and the first-generation YW01 lead compound as well as fluconazole. Compound B3, which is a para-fluorinated version of the studied B-series template, was found to have MICs of 0.125, 0.0625, 0.0625, and 0.5 µg mL-1 in that order. Compound B9 was shown to possess MICs of 0.125, 0.0625, 0.0625, and 0.25 µg mL-1. These very low MICs for compounds B3 and B9 are in stark contrast to the MICs reported for YW01 in the later publication (8, 8, 4, and 32 µg mL-1).

TABLE VI. PUBLISHED ANTIFUNGAL MIC VALUES, µg mL−1, FROM GAO ET AL. [13]

Compound	C. alb. I	C. alb. II	C. trop.	C. parap.	GM-MIC
A7	16	16	8	32	16.000
A8	0.5	0.5	1	1	0.707

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Compound	C. alb. I	C. alb. II	C. trop.	C. parap.	GM-MIC
B1	0.5	0.5	4	1	1.000
B3	0.125	0.0625	0.0625	0.5	0.125
B4	0.25	0.25	8	2	1.000
B5	0.25	0.125	0.125	0.5	0.210
B7	0.5	0.25	0.25	0.5	0.354
B8	0.25	0.25	0.125	1	0.297
B9	0.125	0.0625	0.0625	0.25	0.105
B10	0.125	0.0625	0.0625	0.5	0.125
YW01	8	8	4	32	9.514
Fluconazole	0.5	1	0.5	2	0.841

The MIC values for the selected rows in the table span from 0.0625 to 32 micrograms per milliliter. These values represent actual amounts of a drug (not relative amounts of drug) and do not relate to how well the drug interacts with the target site, predicted affinity to the target site, or size of the inhibition zone. The data columns for the two strains of C. albicans are both included in the table because there may be biologically relevant differences in data collected for each strain. The geometric mean is simply a four-value arithmetic transformation of published data. As such, the user can verify the accuracy of the data in Table VI by entering any individual row from Table VI into Equation (4) of this paper.

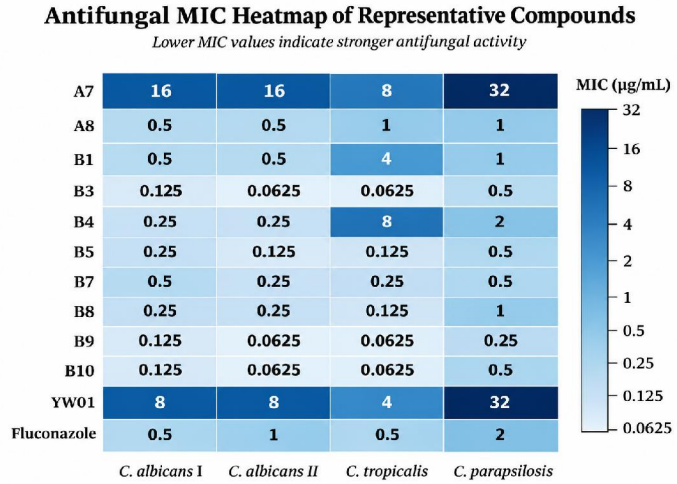

Fig. 6. Heat map of published four-organism MIC values from the single assay series [13].

E. Within-assay potency comparisons

The relative numerical differences in a direction that can be easily understood are measured by the MIC ratio calculated using Equation (5). For the four assay columns, the fluconazole/B3 ratios are 4, 16, 8, and 4. Similarly, for the four assay columns, the fluconazole/B9 ratios are 4, 16, 8, and 8. Therefore, both compounds have lower reported MICs than fluconazole in each of the four listed comparisons; however, the degree to which they provide an advantage over fluconazole varies depending on the organism and the compound's structure. These ratios reflect an in vitro finding based on a single published study's experimental protocol, and do not represent any clinical benefits.

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TABLE VII. WITHIN-STUDY FLUCONAZOLE-TO-COMPOUND MIC RATIOS [13]

Compound	C. alb. I	C. alb. II	C. trop.	C. parap.
A8	1x	2x	0.5x	2x
B1	1x	2x	0.125x	2x
B3	4x	16x	8x	4x
B4	2x	4x	0.0625x	1x
B5	2x	8x	4x	4x
B7	1x	4x	2x	4x
B8	2x	4x	4x	2x
B9	4x	16x	8x	8x
B10	4x	16x	8x	4x

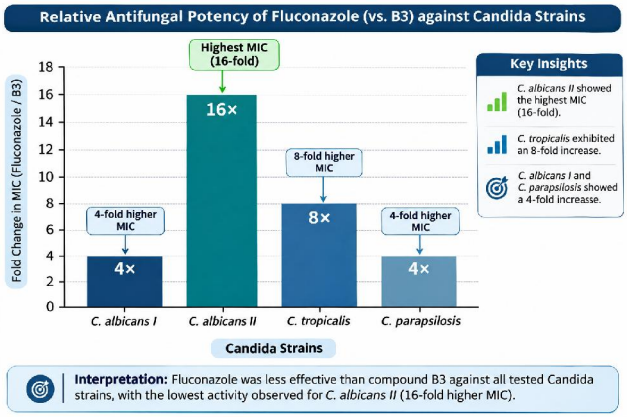

Fig. 7. Published fluconazole/B3 MIC ratios from four matched test conditions [13].

The use of positional substitutions will provide further understanding. Against C. tropicalis, the 2-fluoro analog B1 has MIC 4 µg mL-1; whereas the 4-fluoro analog B3 has MIC 0.0625 µg mL-1, providing a 64-fold difference in MIC. The ratios for C. albicans I and II are 0.5/0.125 = 4 and 0.5/0.0625 = 8 respectively. Therefore, it appears that the location of the fluorine atom, rather than the chemical composition of the molecule, is a key factor within this chemical structure. This result supports the molecular-descriptor observation that positional isomers may have the same scalar formula-based properties, yet different spatial recognition.

B3 and B9 each have three of the same MIC values reported. However, B9 reports 0.25 µg mL−1 instead of 0.5 µg mL−1 for activity against C. parapsilosis. The one dilution step difference between these two reports is a direct consequence of the inherent two-fold variation associated with the broth dilution methodology. While it may be acceptable to list the specific concentration, a separate biological ranking system should include the distribution of replicates, the number of strains tested, and a formal evaluation of target selectivity based upon more than just a single endpoint table.

VI. DISCUSSION

A. Reaction chemistry and green-chemistry boundaries

The advantages of multi-component synthesis are obvious; the same reaction-engineering advantages (bond formation and ring closure) are achieved within the same reaction vessel, and ideally, the only net molecular by-product formed during the chemistry will be water. These benefits are consistently shown through the AE calculations for all substituents tested. However, the excess amounts of ammonium acetate and purification solvents used in the actual synthesis create a significant discrepancy between atom economy and total material used. While the 85-89% yields

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reported by the supported-acid method are promising as source-reported outcomes, increased yields do not necessarily equate to reduced waste production or energy consumption.

The supported-acid method, the use of ethanol to recrystallize products, the use of copper as a catalyst, the application of LED technology, and the use of deep-eutectic media are to be compared to each other on the same basis in terms of mass, purity, and usefulness. The supported-acid study reports that the first step in the reaction is solvent-free, although the recrystallization of products with ethanol is reported as a downstream step in the process [4]. The ethanol reflux route does not require the addition of any catalysts; however, it uses a liquid reaction medium [3]. Copper-catalyzed processes have altered reaction times but require metal-handling procedures [5]. LED-based processing strategies have changed how energy is delivered to reactions [6]. Deep-eutectic processing strategies have created additional factors related to recovering solvents [7]. Comparing these alternatives provides operational justification for performing multi-metric sustainability evaluations, as opposed to selecting a particular route based upon only a single measure of success (yield) or marketing claim (descriptors).

B. Structure, physicochemical properties and antifungal performance

Substitution of the C2 phenyl ring results in predictable changes in both the chemical makeup of a molecule and the estimate of common descriptors. Phenolic hydroxylation produces an increase in polar surface area and donor capacity. Methoxylation produces an increase in acceptor capacity and formula mass. Halogenation typically produces an increase in calculated lipophilicity. These types of property changes may affect solvation, crystal packing, and biological distribution. However, the performance of small-molecule antimicrobials is influenced by many factors. A good example of this is seen in the amide-imidazole biological paper [13], where positional fluoro substitutions create widely varying MIC values even though they have essentially identical elemental compositions and very similar descriptor totals.

The B3 compound in the literature of published anti-fungal studies is chemically different than any of the triarylimidazole compounds (2,4,5-triarylimidazoles) used as part of the computational library. Gao et al. have linked their CYP51-specific compound with further time-kill studies, morphological studies and cell viability studies [13]. It would be a chemical misattribution to assume that the same CYP51 interaction or the same MIC profile could be attributed to a triarylimidazole compound that has been characterized only through its formula and cLogP. Therefore, this study utilizes the published anti-fungal data as independent controls for comparison and does not utilize numerical transfers from one series to another.

C. Reproducibility of the numerical analysis

Every panel containing numbers has a declared origin and a specific transformation applied. Table IV displays results from experiments as reported in [4] along with other physical signatures reported in [4]. Table V calculates charges (in mmoles) using the results displayed in Table IV. Table III calculates molecular descriptors based upon SMILES graph representations of chemicals and identifies the chemical structure and software version used for calculating the transformation. Tables VI-VII report reported MIC values from [13] and apply transformations to them. All of the figures use the exact same data as the tables so there will be no inconsistencies between what is labeled in the figure and what is listed in the table.

When comparing results from multiple laboratories or using different assay techniques, you will need to take into account strain type, growth media used, and how the end point was determined. While the World Health Organization (WHO) priorities classify clinical urgency [1], both the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide guidelines that describe laboratory comparability [16]–[18]. None of these organizations provide substitutes for compound-specific testing. To determine an effective ranking of antifungals based upon concentration, biological variability, target engagement, and selectivity, rather than relying solely on a single computed docking pose or a single calculated physical-chemical parameter.

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VII. TECHNICAL QUALITY AND VALIDATION CRITERIA

The chemical identity records provide a direct linkage between the product code (or other identifier) and the starting aldehyde; reaction conditions used; isolated mass; melting point range; and characterization. Functional group assignments are confirmed by infrared bands; aromatic and substituent environments are verified by nuclear magnetic resonance (NMR); and formulas are confirmed by mass spectrometry (MS) with appropriate instrumentation mass accuracy. Independent of being chemically pure, it is also important that chemical purity does not interfere with the assignment of activity to the target molecule. Residual salts or starting materials may mask effects on growth, making it difficult to attribute activity to the intended target molecule. Table IV provides an example of a good baseline for documenting synthetic data, while the computational matrix provides the fixed constitutional structures.

Standardized testing for yeasts must be internally consistent with the selected CLSI or EUCAST methodology [16]-[18] regarding concentration series, isolate collection identifier, culture medium, inoculum, growth control, solvent control, reference antifungal, and endpoint interpretation. MIC values are naturally evaluated using dilutions; for example, a two-fold concentration series such as 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16 and 32 µg mL−1. It is important to distinguish MIC from MIC50 and inhibition zone diameter since they have different measurement meanings.

Environmental performance is also improved by using physical units when reporting quantities instead of relying on narrative descriptions. Mass of raw inputs, volume and recovery of reaction solvent, volume and recovery of recrystallization solvent, mass of catalyst added, mass of final product, and mass of residue left after cleaning are used to calculate the Process Mass Intensity. The Energy Intensity is calculated based on the amount of energy consumed by the heating/lighting system (Power × Time). A Lifecycle Evaluation considers the environmental impacts associated with the production of raw materials (feedstock) and how the waste stream will be handled (treatment/reuse). These levels illustrate the parameters that the AE and currently proposed charged reagent calculations consider, as well as those that ultimately determine the sustainability of the entire manufacturing process [19], [20], [21].

VIII. INTEGRATED QUANTITATIVE CASE ANALYSES

A. A one-millimole material accounting case

The synthesis of triphenylimidazole reported by its authors can be described as a complete and verifiable 1.00 millimole chemical accounting example. A perfectly balanced equation would show that the elements in benzil and benzaldehyde contribute C21H16O3, and that two ammonia molecules provide two nitrogen atoms and six hydrogen atoms. The resulting product is formula C21H16N2; the three oxygen atoms that were lost during the reaction combine with six hydrogen atoms to form three water molecules. This process retains 296.37 milligrams of matter in the final product and produces approximately 54.05 milligrams of water for each millimole of stoichiometric conversion. The combined total mass of the products equals (to within reasonable limits) the total mass of the reactants, which was determined to be 350.41 milligrams.

The 3 mmol ammonium acetate charge as reported by the literature alters the true loading base: 210.23 mg benzil, 106.12 mg benzaldehyde and 231.25 mg ammonium acetate are added together for the denominator of the reagents. These three reagents equal 547.60 mg. An isolated yield of 89% (as reported) yields 263.77 mg of product on a formula basis. Therefore, the charge efficiency is 48.17%, and the atom economy would ideally be 84.58%. The 36.41 percentage point difference in the two efficiencies is due to the difference in the numerators and input boundary conditions; this does not represent the direct amount of hazardous waste generated. The extra ammonium acetate includes acetate species whose mass is not included in the simplified ammonia based net equation.

TABLE VIII. CALCULATED ONE-MILLIMOLE MASS LEDGER FOR A1 [4]

Mass ledger item	Quantity	Basis
Benzil loaded	210.23 mg	1.00 mmol
Benzaldehyde loaded	106.12 mg	1.00 mmol
Ammonium acetate loaded	231.25 mg	3.00 mmol
Total charged reagents	547.60 mg	Sum of above

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Mass ledger item	Quantity	Basis
Ideal product	296.37 mg	100% conversion
Product at published yield	263.77 mg	89% of ideal
Theoretical water	54.05 mg	3.00 mmol, net equation

The mass ledger may be easily transferred to each of the remaining three sources reported products through the substitution of the aromatic aldehyde and product formula mass and maintaining the documented 1:1:3 charge ratio. A key point of difference will follow: The calculated A1 product mass of 263.77 mg is reported to two decimal places for transparency of arithmetic; however, the original study rounded its experimental isolated mass to 0.26 g. Both represent differing levels of precision for the same reported 89% yield, as opposed to representing two separate experimental results.

B. Four-organism MIC response as a dilution-series case

The Gao et al. study provides another clearly defined biological example. In the case of B3, the sequential MICs are: 0.125; 0.0625; 0.0625; and 0.5 µg mL−1. The multiplication of these MICs results in a value of 0.000244140625 in the same fourth-power unit as the MIC values; the fourth root of this value is equal to 0.125 µg mL−1. With respect to the comparator fluconazole, the calculation is as follows: 0.5 × 1 × 0.5 × 2 = 0.5; the fourth root of 0.5 is 0.841 µg mL−1 (to three decimal places). Therefore, the within-panel ratio of the geometric means of the two compounds is: 0.841 / 0.125 = 6.73. This ratio represents the geometric mean of the four pairs of MIC ratios: [4, 16, 8, 4] and therefore represents a internal arithmetic check on Table VII.

Logarithmically, using base two, the four comparisons made in B3 represent 2, 4, 3, and 2, respective twofold dilutions from the fluconazole concentration. The average dilution step was 2.75, which corresponds to a multiplication factor of 2^2.75 = 6.73. Similarly, when checking the B9 results, there were four pairs of values [4, 16, 8, 8], resulting in a geometric factor of 8.00. While these transformations can provide a compact representation of observations within studies, the original four MIC columns must be retained to maintain species-specific differences. An overall positive result may mask a negative result with respect to a single species; thus, the original endpoints and the transformed value are always reported together.

C. Practical meaning of positional isomer comparisons

The 2-fluoro and 4-fluoro entries in Gao et al.'s B series demonstrate the effect of position-dependent substitutions on spatial orientation. B1 has values of 0.5, 0.5, 4 and 1 microgram per milliliter (ug mL-1), while B3 has values of 0.125, 0.0625, 0.0625 and 0.5 microgram per milliliter (ug mL-1). Both molecules have a fluoro group attached to them; however, the different locations where the fluoro group attaches to the molecule alter the way the molecule interacts with the biological systems. The relative differences are 4, 8, 64 and 2 times larger than the MIC column for B1 and B3 respectively. The 64-fold difference in activity against C. tropicalis provides valuable insight into how spatial orientation affects biological activity, as the position-dependence of this effect was demonstrated using the same chemical research series and assay methodology, thereby providing a more interpretable comparison of the positions as opposed to combining results from unrelated literature studies.

The calculated triarylimidazole matrices contain matched regioisomer sets: IM02-IM04, IM05-IM07, and IM08-IM10. Within each of these three-member groups, the molecular formulas, molecular weights, calculated LogP values (cLogP), and total polar surface areas (TPSA) are identical. Therefore, a descriptor model using only scalar variables would assign the same feature values to every regioisomer regardless of the position of the substituent. This provides an excellent example as to why it may be beneficial to utilize atom-level molecular graphs, shape-dependent descriptors, and/or conformer information when evaluating the isomer-dependent biological activities of compounds. Additionally, this illustrates why it is necessary to verify compound nomenclature and exact substituent positions prior to utilizing spectral and pharmacological data obtained from published chemical literature.

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The two cases (mass-ledger and dilution-series) provide different types of contribution. The material-balance analysis provides information on how much reagent is used and what is the isolated yield. This will allow us to see how each affect the resource efficiency of the reaction. The within-study MIC analysis provides information on how the position of substituents and the type of fungus used will affect the reported biological concentrations. For both analyses, we have explicit equations, unambiguous units and traceable original observations which are more useful than a single overall score.

IX. SCOPE OF INTERPRETATION

The quantitative research incorporates three separate data sets: two experimental and one computed structural series. One experimental data set provides isolated product outcome for each of the four triarylimidazoles in the same silica supported reaction conditions [4]. The other experimental data set provides experimentally determined MIC values for an additional amide-imidazole structural family using a shared yeast assay [13]. Cross-study discussions are limited to methodological issues. The major numerical interpretation (mass efficiency and within study MIC ratio) is obtained from the exact source records and equations as discussed above.

Molecular cLogP and TPSA summarize molecular fragments rather than a three-dimensional protein-ligand interaction, and the model does not attempt to convert them into MIC predictions. The tabulated potency differences represent specific laboratory strains and an in vitro endpoint; they cannot establish human efficacy, pharmacokinetics or broad-spectrum susceptibility. The analysis is therefore strongest as a reproducible link between green synthetic chemistry, explicitly identified chemical structures, and published biological evidence that has been correctly delineated.

X. CONCLUSION

This study provided a viable technical path to developing eco-friendly imidazoles using an established SiO2-NaHSO4 reaction that produced four characterized triarylimidazoles (85-89% isolated yield) when heated to 120 °C for 30 min [4]. Twelve 2,4,5-triarylimidazole molecular graphs were standardized and computationally evaluated; results showed formula mass ranges from 296.37 - 356.43 g/mol, cLogP ranges from 5.12 - 6.06 and TPSA ranges from 28.68 - 48.91 Å2. While the uncharged framework yields 84.58% theoretical atom economy, the charged-reagent based calculation yields about 48.17% of atoms used in achieving the highest yield record of 89%. Therefore, reporting both atom conservation and actual reagent consumption is necessary.

The independent comparative study of antifungal agents, as reported in [13], demonstrated that B3 had minimum inhibitory concentration (MIC) values of 0.125, 0.0625, 0.0625 and 0.5 µg mL-1 for each of the four designated Candida test panels. For all panels, B3's MIC values were from 4- to 16-fold less than those for fluconazole. The main scientific conclusion is the clear differentiation among the scaffold-based chemical calculation results, experimentally published synthetic procedures and compound-specific published antifungal activity. This differentiation provides quantifiable conclusions while avoiding confusion among different structural types of imidazole chemistry.

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