Phenyl Thiourea-Bis(indolyl)methane Hybrids as Potential Antifungal Agents: Design, Synthesis, and In Silico Pharmacokinetic studies

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Abstract
A series of Bis(indolyl) methanes thiourea conjugates (5a-5h) was synthesized via a three step sequence. The core scaffold was constructed through acid-catalysed condensation in refluxing acetic acid, followed by reduction using sodium borohydride heptahydrate and nickel acetate. Reaction of the intermediate with various arylisothiocyanates in acetone afforded the compounds. Compounds (5a-5h) were characterized by proton nuclear magnetic resonance (1H-NMR and 13C-NMR), High resolution mass spectroscopy (HRMS) and Fourier transform infrared (FTIR) spectroscopy. Antifungal activity of conjugates (5a-5h) was assessed against four fungal strains, namely Aspergillus niger, Aspergillus fumigatus, Candida parapsilosis, and Candida albicans, employing well diffusion assay. Some conjugates exhibited antifungal activity. Compound 5g and 5f demonstrated the highest efficacy 2-fold better than standard drug and 5a exhibited almost equal to the standard. Additionally, in silico evaluations of physicochemical parameters, including lipophilicity, and pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME), of the synthesized compounds were conducted. Structure-activity relationships (SAR) reveal that lipophilic, electron-withdrawing iodo (5g) and trifluoromethyl (5f) substitutions greatly improve broad-spectrum antifungal effectiveness, outperforming Fluconazole. In silico ADME profiling verifies that these variants possess favorable drug-like characteristics, maintaining rigidity (≤9 rotatable bonds) and membrane permeability (TPSA=87.73 A˚2).

Keywords: Bis(indolyl)methane-thiourea conjugates, In vitro Antifungal , In silico ADME,SAR Study.
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1. Introduction

Recently, systemic and superficial fungal infections have increased, posing a global public health threat. This rise is mainly due to more immunocompromised individuals, such as those undergoing chemotherapy, organ transplants, with HIV/AIDS, and in intensive care. Opportunistic yeast species like Candida albicans and Candida parapsilosis cause hospital-acquired fungemia, while Aspergillus niger and Aspergillus fumigatus are linked to severe aspergillosis [1]. Despite their impact, antifungal treatments are limited to azoles, polyenes, and echinocandins, leading to multidrug-resistant strains [2].Current antifungal medications are constrained by narrow therapeutic ranges and significant toxicity, necessitating the development of new compounds with innovative mechanisms. Molecular hybridization, which combines pharmacophores to achieve synergistic effects, presents a promising approach. Among nitrogen-containing heterocycles, the indole nucleus is particularly valued for its versatility [3]. Heterocyclic conjugates play a pivotal role in the treatment of a wide variety of diseases such as cancer, infection, inflammation and neurological disorders, thus leveraging the structural diversity and biological relevance of heterocycles found in nature and several FDA-approved drugs[4].

Bis(indolyl)methanes(BIMs), characterized by two indole rings by a carbon spacer, have attracted considerable interest [5]. Derivatives of BIMs demonstrate antibacterial, anticancer, anti-inflammatory, and antimicrobial properties[6].The lipophilic core of the BIM structure facilitates hydrophobic interactions with microbial targets, while the thiourea group (-NH-CS-NH-) plays a pivotal role in drug design [7]. This moiety functions as both a hydrogen bond donar and acceptor, interacting with enzymes and receptors, while the thiocarbonyl group [C=S] enhance permeability. Modified thiourea and thioether derivatives exhibit antifungal properties by inhibiting pathways or disrupting cell walls [8,9]. Building on these insights, we present the design, synthesis and evaluation of novel thiourea-Bis(indolyl)methane hybrids [10]. The linkage of the BIM core to the thiourea moiety establishes a framework for growth inhibition. This

study details the synthesis and characterization of these conjugates [11,12]. We evaluate their antifungal efficacy against filamentous (A. niger, A. fumigatus) and yeast like (C. parapsilosis, C.albicans) pathogens using a well diffusion assay [13].We also present an in silico screening of their physicochemical and biopharmaceutical profiles, focusing on lipophilicity and ADME parameters [14].

2. MATERIAL AND METHODS

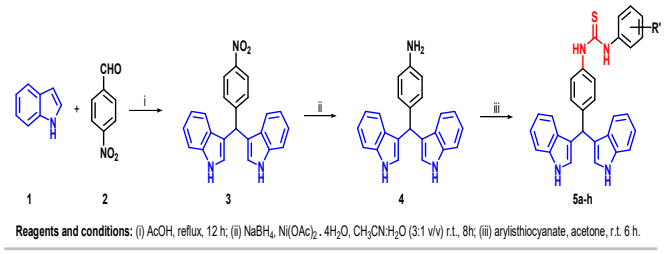
2.1 Materials

The reaction was monitored using thin-layer chromatography (TLC), and melting points were determined using the open capillary method, with no corrections applied. All reagents and solvents were procured from Spectrochem and Himedia. The ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVANCE-III 400 spectrometer (Osmania university-Hyderabad) at 25°C, with DMSO-d_6 serving as the solvent and TMS as the internal standard. FTIR spectra were obtained using a Thermo Fisher Scientific Nicolet iS50 FTIR spectrophotometer (IIT-Hyderebad) and High-resolution mass spectrometry (S.R.T.M.University-Nanded) was conducted employing electrospray ionization (ESI-QTOF) in positive mode. The reaction was monitored using TLC and Melting points were determined using the open capillary method and are uncorrected

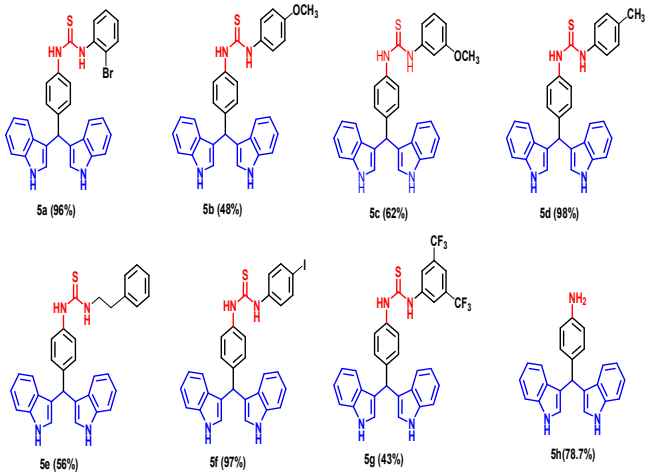
2.2 Experimental

The synthesis of Bis(indolyl)methanes amine intermediate is outlined in below mentioned Scheme. Precursor compounds 3 and 4 were synthesized as shown. The 4-nitro bis(indolyl)methanes were produced from two equivalents of indole and one equivalent of 4-nitro benzaldehyde, To convert BIM nitro to BIM amine, four equivalents of sodium borohydride and 0.2 equivalents of nickel acetate heptahydrate were used in 150 mL of acetonitrile and water (3:1 ratio). The reaction, conducted at ambient temperature, was monitored via TLC and completed in eight hours. The mixture was transferred to a separating funnel, where dichloromethane (DCM) was added, but layers didn't separate well until a small amount of sodium chloride (NaCl) was introduced. The organic layer was extracted three times, then transferred to a round-bottom flask, and the solvent was removed with a rotary evaporator. The compound was isolated, dried, and pure product obtained using diethyl ether. Structures were confirmed by ^{1}H-NMR, ^{13}C-NMR, and High resolution mass spectrometry.

Scheme-1



Reagents and conditions: (i) AcOH, reflux, 12 h; (ii) $NaBH_4$, $Ni(OAc)_2 . 4H_2O$, CH_3CN:H_2O (3:1 v/v) r.t., 8h; (iii) arylisthiocyanate, acetone, r.t. 6 h.



1) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-(2-bromophenyl)thiourea-(5a)

Solid; Yield- 96% ; ^{1} H NMR (400 MHz, DMSO) δ ppm 10.82 (s, 2H), 9.96 (s, 1H), 9.29 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H),7.56 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.32 (dd, J = 17.6, 7.1 Hz, 7H), 7.16 (t, J =7.5 Hz, 1H),7.03 (t, J = 7.3 Hz, 2H), 6.91 – 6.81 (m, 4H), 5.82 (s, 1H). ^{13} C NMR (101 MHz, DMSO) δ ppm 180.48,137.05, 133.07, 132.95, 130.64, 128.90, 128.28, 127.07, 124.03, 123.95, 121.36, 119.58, 118.65,118.51, 111.92, 40.58, 40.37, 40.16, 39.95, 39.74, 39.53, 39.32. ESI-HRMS Anal Caltd for C 30 H 24 BrN 4 S [M+H] + : 551.0905 ,Obtained 551.0258.

2) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-(4-methoxyphenyl)thiourea-(5b)

Solid; Yield- 48%; ^{1} H NMR (400 MHz, DMSO) δ ppm 10.84 (s, 2H), 9.61 (dd, J = 49.4, 32.7 Hz, 1H), 7.49 – 7.23 (m, 10H),7.05 (t, J = 7.3 Hz, 2H), 6.92 –

6.76 (m, 7H), 5.83 (s, 1H), 3.75 (s, 3H). 13 C NMR (101 MHz, DMSO) δppm 207.10, 180.21, 169.22, 156.99, 141.60, 137.63, 137.05, 132.72, 128.70, 127.09, 126.56,124.01, 123.86, 123.80, 121.36, 119.60, 118.66, 118.59, 114.10, 111.92, 64.85, 55.69, 40.56,40.35, 40.14, 39.93, 39.72, 39.51, 39.30, 31.15, 14.55 ESI-HRMS Anal Caltd for C 31 H 27 N 4 OS,[M+H] + : 503.1906 , Obtained:503.1884.

3) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-(3-methoxyphenyl)thiourea-(5c)

Solid; Yield- 62% ; ^{1}H NMR (400 MHz, DMSO) δppm 10.83 (s, 2H), 9.74 (s, 2H), 7.34 (d, J = 11.1 Hz, 8H), 7.19 (d, J = 22.3 Hz, 2H), 7.03 (d, J = 8.7 Hz, 3H), 6.85 (s, 4H), 6.70 (d, J = 6.5 Hz, 1H), 5.82 (s, 1H), 3.73 (s, 3H). C31H27N4OS,Exact Mass: 503.1906 , Obtained:503.1882

4) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-p-tolylthiourea-(5d)

Solid; Yield- 98%; ^{1} H NMR (400 MHz, DMSO) δ 10.84 (s, 2H), 9.71 (s, 2H), 7.40 (d, J = 11.9 Hz, 3H), 7.35 (d, J= 8.5 Hz,5H), 7.29 (s, 2H), 7.13 (d, J = 6.6 Hz, 2H), 7.06 (t, J = 7.1 Hz, 2H), 6.89 (d, J = 12.5 Hz, 4H), 5.84 (s,1H), 2.28 (s, 3H). 13 C NMR (101 MHz, DMSO) δ ppm 179.91, 141.63, 137.62, 137.35, 137.06, 134.11,129.64, 129.35, 129.33, 128.70, 127.10, 124.41, 124.37, 124.01, 123.87, 123.76, 121.37, 119.60, 118.66,118.59, 111.93, 55.36, 40.56, 40.35, 40.14, 39.93, 39.72, 39.52, 39.31, 31.15, 20.99.ESI-HRMS Anal Caltd for C 31 H 27 N 4 S [M+H] + : 487.1956,Obtained: 487.1935.

5) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-phenethylthiourea-(5e)

Solid; Yield- 56% ; ^{1} H NMR (400 MHz, DMSO) δ ppm 10.84 (s, 2H), 7.62 (s, 1H), 7.30 (s, 8H), 7.23 (s, 4H), 7.04 (s, 2H),6.87 (s, 4H), 5.81 (s, 1H), 3.69 (s, 1H), 2.86 (s, 3H). 13 C NMR (101 MHz, DMSO) δ ppm 139.76,137.03,129.12, 128.85, 127.07, 126.61, 123.98, 121.36, 119.57, 118.65, 118.55, 111.91, 40.55, 40.35, 40.14,39.93, 39.72, 39.51, 39.30, 34.91.ESI-HRMS Anal Caltd for C 32 H 29 N 4 S[M+H] + : 501.2113 , Obtained:501.1964.

6) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-(4-iodophenyl)thiourea-(5f)

Solid ;Yield- 97% ; 1 H NMR (400 MHz, DMSO) δ ppm 10.83 (s, 2H), 9.81 (d, J = 17.0 Hz, 2H), 7.65 (d, J = 7.9Hz, 2H),7.33 (dd, J = 14.6, 6.3 Hz, 10H), 7.04 (t, J = 7.3 Hz, 2H), 6.88 (d, J = 10.9 Hz, 4H), 5.82 (s, 1H). 13 CNMR (101 MHz, DMSO) δ ppm 137.59, 137.47, 137.02, 128.77, 127.07, 126.23, 123.98,123.80, 121.35, 119.57, 118.65, 118.52, 111.91, 40.57, 40.36, 40.15, 39.94, 39.73, 39.52, 39.31,31.16.12)

7) 1-(4-(di(1H-indol-3-yl)methyl)phenyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea-(5g)

Solid; Yield- 43% ; ^{1} H NMR (400 MHz, DMSO) δ ppm 10.82 (d, J = 12.3 Hz, 2H), 8.44 – 8.19 (m, 2H), 7.45 (d, J= 6.8 Hz,12H), 7.38 – 7.18 (m, 4H), 7.02 (d, J = 5.9 Hz, 1H), 6.83 (d, J = 21.9 Hz, 2H), 5.82 (s, 1H). ^{13}C NMR(101 MHz, DMSO) δ ppm 141.57, 137.03, 127.07, 124.00, 121.30, 119.57, 118.55, 111.90,40.55, 40.35, 40.14, 39.93, 39.72, 39.51, 39.30, 24.54.ESI-HRMS Anal Caltd for C 32 H 23 F 6 N 4 S [M+H] + : 609.1548 , Obtained:609.1512.

8) 1-(4-(di(1H-indol-3-yl)methyl) aniline-(5h)

Dark orange solid; Yield- 95.8%; m.p. 230–232 C; ^{1}H NMR (500 MHz, DMSO-d6) d 10.73 (s, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.27(d, J = 7.9 Hz, 2H), 7.07–6.95 (m, 4H), 6.85 (t, J = 7.5 Hz, 2H), 6.78 (d, J = 1.8 Hz, 2H), 6.48 (d, J = 8.3 Hz, 2H), 5.63 (s, 1H), 4.82 (s,2H);

2.3 Biological Analysis

2.3.1 Preparation of Inoculum

For antifungal assays, A. niger, A. oryzae, C. albicans were cultured on PDA plates at 28 ± 2°C for 48–72 hours. Fungal spores and yeast cells were harvested using saline (0.85% NaCl) with 0.1% Tween 80. Inoculum density was ~1 × 10^{6} spores or cells/mL.

2.3.2 Spread Plate Inoculation

100 µL of fungal suspension was spread on PDA plates for even spore or yeast cell distribution.

2.3.3 Preparation and Application of Chemical Compound

The test compound was dissolved in a sterile solvent (e.g., DMSO, distilled water) to desired concentrations. Solutions were sterilized via a 0.22 µm membrane filter. After inoculation, 6–8 mm wells were punched into agar using a sterile cork borer, and agar plugs were removed. 50–100 µL of compound solution at various concentrations was added to each well. The solvent served as the negative control. Streptomycin and fluconazole were positive controls. Plates were at room temperature for 30–60 minutes for pre-diffusion. Bacterial plates were incubated at 37°C for 24 hours; fungal plates at 28 ± 2°C for 48–72 hours.Post-incubation, plates were examined for clear zones around wells, indicating antimicrobial activity. The zone diameter was measured in millimeters with a ruler.

2.3.4. ADME Prediction Studies

The ADME analysis of synthesized Compounds Bis(Indolyl) methane thiourea conjugates (5a-5h), was performed using the online tool Swiss ADME to evaluate their pharmacokinetic properties.

3. Results and Discussion

3.1 Invitro Biological evaluation (Antifungal activity)

Table 1 : Antifungal activities of Bis(indolyl)methanes thiourea derivatives **5a-5h**

Name of Compound	Aspergillus niger	Aspergillus fumigatus	Candida parapsilosis	Candida Albicans
5a	13	12	12	12
5b	NZ	14	11	15
5c	12	13	NZ	13
5d	NZ	NZ	13	14
5e	17	17	NZ	12
5f	15	15	18	14
5g	22	21	21	13
5h	10	NZ	20	10
Negative Control	NZ	NZ	NZ	NZ
Positive Control	12	13	12	12

NZ: No zone

pathogens, namely Aspergillus niger, Aspergillus fumigatus, Candida parapsilosis, and Candida albicans using the agar well diffusion method. The antifungal efficacy was determined by measuring the zone of inhibition in millimetres, while "NZ" indicated no detectable antifungal activity. Fluconazole was used as the positive control and the negative control showed no inhibition against any of the tested organisms. Among all the tested compounds, compound 5g exhibited the highest antifungal activity against all fungal strains, producing inhibition zones of 22 mm against A. niger, 21 mm against A. fumigatus, 21 mm against C. parapsilosis, and 13 mm against C. albicans. Fluconazole was employed as the positive control, whereas the negative control exhibited no inhibitory effect on any of the tested organisms. Among the compounds assessed, compound 5g demonstrated the most potent antifungal activity across all fungal strains, with inhibition zones measuring 22mm for A. niger, 21mm for A. fumigatus, 21mm for C.parasilosis, and 13mm for C.albicans. These results indicate that compound 5g possesses broad spectrum antifungal capabilities and was notably more effective than the positive control for most fungi tested. Compound 5f also displayed significant antifungal properties, especially against C.parapsilosis with an 18mm inhibition zone, followed by 15mm for both A.niger and A. fumigatus, and 14 mm for C. albicans. Similarly, compound 5e exhibited good efficacy against filamentous fungi, achieving inhibition zones of 17mm for both A.niger and A. fumigatus, although it was inactive against C.parapsilosis. Compounds 5a and 5c showed moderate antifungal activity. Compound 5a consistently produced inhibition zones of 12-13mm across all organisms tested, whereas compound 5c was effective against A. niger, A. fumigatus, and C. albicans, but not against C. parapsilosis. Compound 5d was inactive against both Aspergillus species but demonstrated moderate activity against Candida species, with inhibition zones of 13mm and 14mm for C.parapsilosis and C.albicans respectively. Compound 5h exhibit selective antifungal activity, strobgly inhibiting C. parapsilosis (20 mm)but showing weak or no activity against other antifungal strains. Compound 5b was active against A. fumigatus, C. parapsilosis, and C. albicans with no inhibition was observed against A.niger. The fluconazole resulted in inhibition zones of 12–13 mm for all fungi tested. Notably, several synthesized compounds, especially 5g, 5f, 5e and 5h demonstrated superior antifungal activity compared to the standard drug against certain pathogens. Overall the findings suggest that substitution patterns in the synthesized compounds significantly influenced antifungal activity, and compounds such as 5g and 5f could be promising candidates for further antifungal research.

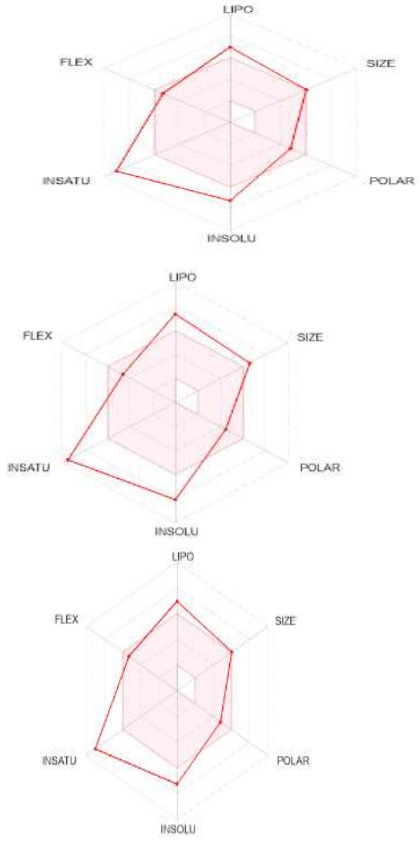
3.2 Physicochemical and In Silico ADME Profiling

An in silico analysis was conducted to assess the drug-likeness and pharmacokinetic potential of synthesized conjugates (5a-5h). The molecular weight (Mw) of the thiourea derivatives (5a–g) varied between 486 and 608 g/mol. The active halogenated variants, 5f (608 g/mol) and 5g (598 g/mol), slightly surpass Lipinski's 500g/mol threshold, yet their effectiveness justifies the additional mass. The topological polar surface area (TPSA) for most compounds (5a, 5d–5g) was 87.73 Aº2, while the methoxy analogues 5b-5c measured 96.96 Aº2, remaining under the 140 Aº2 limit, indicating strong membrane permeability and absorption. All compounds complied with Veber's rules, demonstrating optimal rigidity with a low no. of rotatable bonds (≤9) and balanced hydrogen bonding (0-1 HBD, 3-6 HBA). These findings confirm that the bulky bis(imdolyl)methane thiourea framework retains favourable pharmacokinetic properties.

Table 2: Physicochemical properties of the synthesized compounds (5a-5h)

compound	Formula	Mw	Heavyatoms	Aromatic Heavyatoms	Fraction Csp3	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
5a	C30H23BrN4S	551	36	30	0.03	7	0	4	157.72	87.73
5b	C31H26N4OS	502	37	30	0.06	8	1	4	156.51	96.96
5c	C31H26N4OS	502	37	30	0.06	8	1	4	156.51	96.96
5d	C31H26N4S	486	36	30	0.06	7	0	4	154.98	87.73
5e	C32H28N4S	500	37	30	0.09	9	0	4	158.09	87.73
5f	C32H22F6N4S	608	43	30	0.09	9	6	4	160.02	87.73
5g	C30H23IN4S	598	36	30	0.03	7	0	4	162.74	87.73
5h	C23H19N3	337	26	24	0.04	3	0	3	108.5	57.6

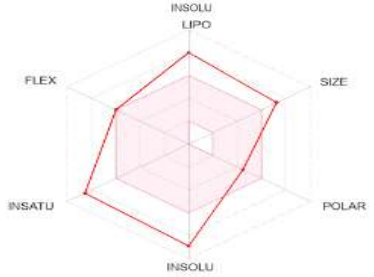
The bioavailability radar plots of the synthesized compounds (5a-5h) obtained from Swiss ADME tool.



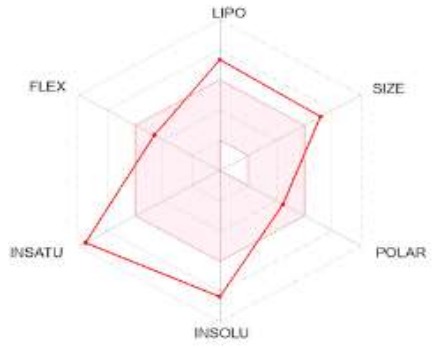
5a 5b 5c

5d

5e



5f



5g

5h

3.3 SAR Study

The Structure-Activity Relationship(SAR) analysis of bis(indolyl)methane thiourea derivatives reveals that modifications to the peripheral ring effect the balance between antifungal efficacy and pharmacokinetic drug-likeness.The incorporation of heavy liophilic electron-withdrawing halogen groups enhances broad-spectrum efficacy. Notably, compounds 5g and 5f demonstrate superior effectiveness, significantly outperforming the standard drug Fluconazole by facilitating improved penetration of fungal membranes. Conversly, electron donating methoxy groups (5b,5c) restrict the range of activity, resulting in complete inactivity in certain regions(NZ).Hydrophobic alkylation, as seen in 5e, directs selectivity exclusively towards filamentous Aspergillus strains. Reduction of the core structure(5h) eliminates broad spectrum capability but yields highly specialized, potent action against C.parapsilosis. From an ADME perspective, these structural modifications are well-tolerated, maintaining excellent drug-likeness profiles. Although the highly active halogenated variants 5f,5g slightly exceed Lipinski's molecular weight threshold (>500 g/mol), their exceptional biological potency justified the increased mass. Mainly, all thiourea derivatives retain a low no. of rotatable bonds (≤9) and an optimal Topological polar Surface Area (TPSA) of 87.73 Å^2,well below the 140 Å^2 limit. This indicates that the rigid bulky bis(indolyl)methane framework effectively preserves high membrane permeability and oral bioavailability while maximizing the eradication of target fungi.

4. Conclusion: A series of Bis(indolyly) methanes thiourea conjugates was successfully synthesized and their structures were confirmed by spectroscopic data. Among them, compounds 5f exhibited good inhibitory activity against most of the tested fungal strains. Compound 5g was most active amongst the series. It displayed almost 2 fold more potential activity against A. niger ,A.fumigatus, C. parapsilosis compared to the standard drug fluconazole. The ADME parameters in acceptable range confer 5d and 5e to be good drug candidates. Based on the results of antifungal activities and computational studies, these conjugates show great promise as novel antifungal agents. Further, the SAR's and the other ongoing studies related to the biological activity will shed more light on the mechanistic pathways of inhibitory activity in future.

Supporting Information Summary

Experimental details and characterization data of all the synthesized compounds are provided. In addition, supporting information also contains the procedure for in vitro antifungal activity and in silico studies.

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
The data that support the findings of this study are available in the supplementary material of this article.

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