Research Article

Design, Synthesis and Molecular Docking Study of substituted *N*-aminocarbonyl arylvinylbenzamides

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ABSTRACT

In an attempt to find a new class of antimicrobial agents, a series of novel *N*-aminocarbonyl arylvinyl-benzamides **5**(**B1-B28**) were synthesized and evaluated for *in vitro* antifungal activity against *Candida albicans* (NCIM 3471), *Aspergillus niger* (NCIM 545), and *Penicillium chrysogenum* (NCIM 709). The title compounds were synthesized from nucleophilic ring opening of the appropriate arylideneoxazolones **4**(**A1-A3**) using suitable amines. All the compounds were characterized using elemental analytical (C, H, and N) and spectral (FT-IR, ^{1}H NMR, ^{13}C NMR and MS) data. Among the tested compounds, *N*-{(1Z)-3-[(3-nitrophenyl)amino]-3-oxo-1-phenylprop-1-en-2-yl}benzamide **5**(**B22**) was identified as a potentially excellent antifungal agent. It exhibited potent antifungal activity against *Candida albicans* (MIC; 2 μg/mL), *Aspergillus niger* (MIC; 2 μg/mL), and *Penicillium chrysogenum* (MIC; 2 μg/mL) comparable with that of ketoconazole. Also compounds N-[(1Z)-3-[(2-fluorophenyl) amino]-1-(furan-2-yl)-3-oxoprop-1-en-2-yl]benzamide **5**(**B6**) and N-{(1Z)-1-(furan-2-yl)-3-[(3-nitrophenyl) amino]-3-oxoprop-1-en-2-yl} benzamide **5**(**B4**) also displayed good antifungal effects against all fungal strains tested. The binding mode of the tested compounds inside the sterol 14α-demethylase active site was predicted using a docking technique. Lipinski's rule and in silico ADME pharmacokinetic parameters are within the acceptable range defined for human use thereby indicating their potential as a drug-like molecules.

Keywords: Antifungal activity**,** *N*-aminocarbonyl arylvinylbenzamides, arylideneoxazolones, 14α-demethylase, molecular docking, lipinski's rule

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INTRODUCTION

Fungal infections pose a continuing and serious threat to human health and life [1]. These fungous infections in humans can be classified into (a) allergic reactions to fungous proteins, (b) toxic reactions to toxins present in certain fungi, and (c) infections (mycoses). Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and, in certain instances, systemic infections that cause a variety of conditions ranging from athlete's foot and nail infections to severe life-threatening disseminated diseases, e.g., histoplasmosis [2]. Many fungous infections are caused by opportunistic pathogens that may be endogenous (Candida infections) or acquired from the environment (Crypto-coccus, Aspergillus infections) [1].

Invasive fungous infections and dermato-mycoses are another type of fungous infection. They are produced by fungous organisms in individuals with increased vulnerability, such as neonates, cancer patients receiving chemotherapy, organ transplant patients, and burns patients, apart from those with acquired immuno-deficiency syndrome (AIDS).

Other risk factors include corticosteroid and antibiotic treatments, diabetes, lesions of the epidermis and dermis, malnutrition, neutropenia and surgery [3–6]. In recent years, the incidence and severity of fungous diseases have increased, particularly in patients with impaired immunity [7].

Fungal diseases produce considerable alarm among the medical profession. Dermatophyte infections such as tinea pedis and candidiasis, although rarely fatal, are common and widespread throughout the world. Pathogens such as *Candida albicans, Cryptococcus neoformans, Pneumocystis carinii* and *Aspergillus fumigatus* are the causes of considerable morbidity and mortality in immuno-compromised patients [8]. *Aspergillus* and *Candida* species account for the majority of documented infections. Recent epidemiological trends indicate a shift towards infections by *Aspergillus* species, *non-albicans Candida* species and previously uncommon fungi that often have diminished susceptibility to currently used antifungal agents [9–13].

Although, the arsenal of antifungal drugs has expanded, currently available antifungal drugs do not meet the increasing requirements of managing infections in complex patient populations. The development of new antifungal drugs has been constant requirement in clinical therapy [14].

The increased use of antifungal agents has resulted in the development of resistance and toxicity, Furthermore, efficacy rates have dropped. As a result, a new heterocyclic with distinct action for use in multitargeted combination therapy is being searched for [15].

A compound with an amide-bond backbone has a wide range of biologic activities. Among the natural and synthetic substituted amide derivatives, there are compounds possessing anti-proliferative, antiviral, antimalarial, general anesthetics, anti-inflammatory, antimicrobials and in the treatment of Alzheimer's diseases [16]. Benzamide derivatives exhibit various types of biologic properties such as anthelmintic, antihistamines, antifungal, and antibacterial [17]. Benzamide Scaffold incorporated with heterocyclic residue like thiazole, furan and phenyl ring substituted with electron-donating and electron-withdrawing groups were found to prove antifungal activity [17-20]. Furthermore the compounds comprising olefins show good antifungal activity [21, 22]. Hence, in the continuation of our research on antifungal agents, in the present study we synthesized *N*-subtituted benzamides and subjected them to antifungal and molecular docking studies to examine their biological activities, possible interactions and binding patterns with the proteins in relation to their activity.

Chemistry

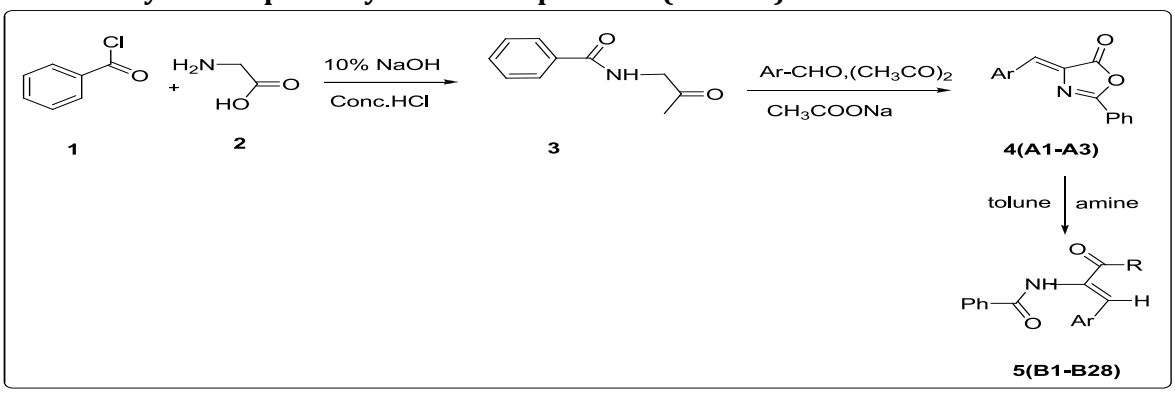
In the present investigations, we have synthesized and characterized the novel *N*-aminocarbonyl arylvinyl benzamide derivatives and explored their antifungal activity. Benzoylglycine (3) was synthesized by reacting benzoyl chloride (1) and glycerin (2) using an established procedure [23]. Arylideneoxazolones **4**(**A1-A3**) were synthesized from benzol- glycine (3), aromatic aldehydes, sodium acetate and acetic anhydride using a method described previously [23]. Finally, these arylideneoxazolones were reacted with primary and secondary amines to the obtain target compounds, namely the benzamides **5**(**B1-B28**) (**Sheme I**). We used microwaves to optimize the reaction.

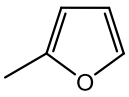
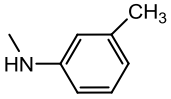
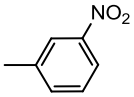
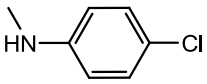
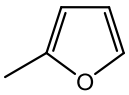
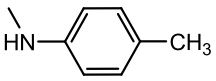
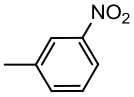
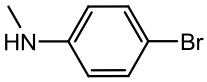
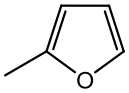
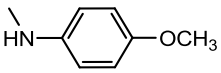
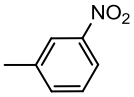
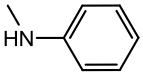
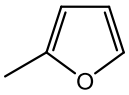
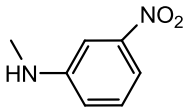
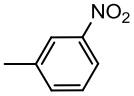
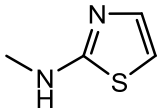
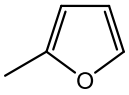
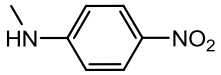
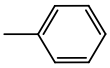
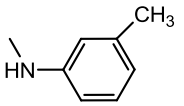
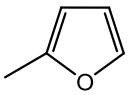
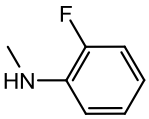
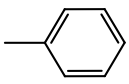
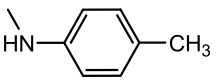
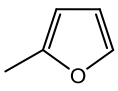
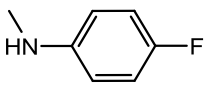
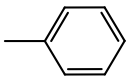
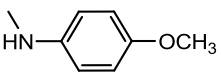
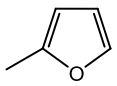
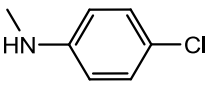
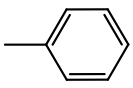
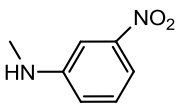
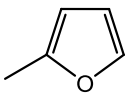
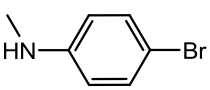
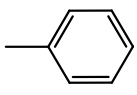
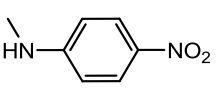
Rationale and Designing

In this study, a new sub family of compounds containing *N*-aminocarbonyl arylvinyl benzamides were investigated as antifungal agents. Our strategy has been directed towards designing a variety of ligands that are structurally similar to the co-crystallized ligand VNI-490, which is a substituted benzamide analog and a novel selective inhibitor of the enzyme lanosterol demethylase. Thus we have designed and synthesized a series of *N*-aminocarbonyl arylvinyl benzamides (B1-B28) in which we have retained the benzamide skeleton as a core to mimic the structure of VNI-490. In additional to the core, new types of substitute group were also investigated. We replaced the oxadiazole ring with that of the furan in the compounds we synthesized just to check the effect of the furan ring on lanosterol demethylase-inhibitory activity. We introduced an electron-withdrawing group on the benzamide core, like the 2,4-dichlorphynyl entity in VNI-490, just to

increase the lipophilicity of the compounds (**Figure 1**).

SCHEME I- Synthesis pathway of title compounds 5(B1-B28)



Compd.	Ar	R	Compd.	Ar	R
5(B1)			5(B15)		
5(B2)			5(B16)		
5(B3)			5(B17)		
5(B4)			5(B18)		
5(B5)			5(B19)		
5(B6)			5(B20)		
5(B7)			5(B21)		
5(B8)			5(B22)		
5(B9)			5(B23)		

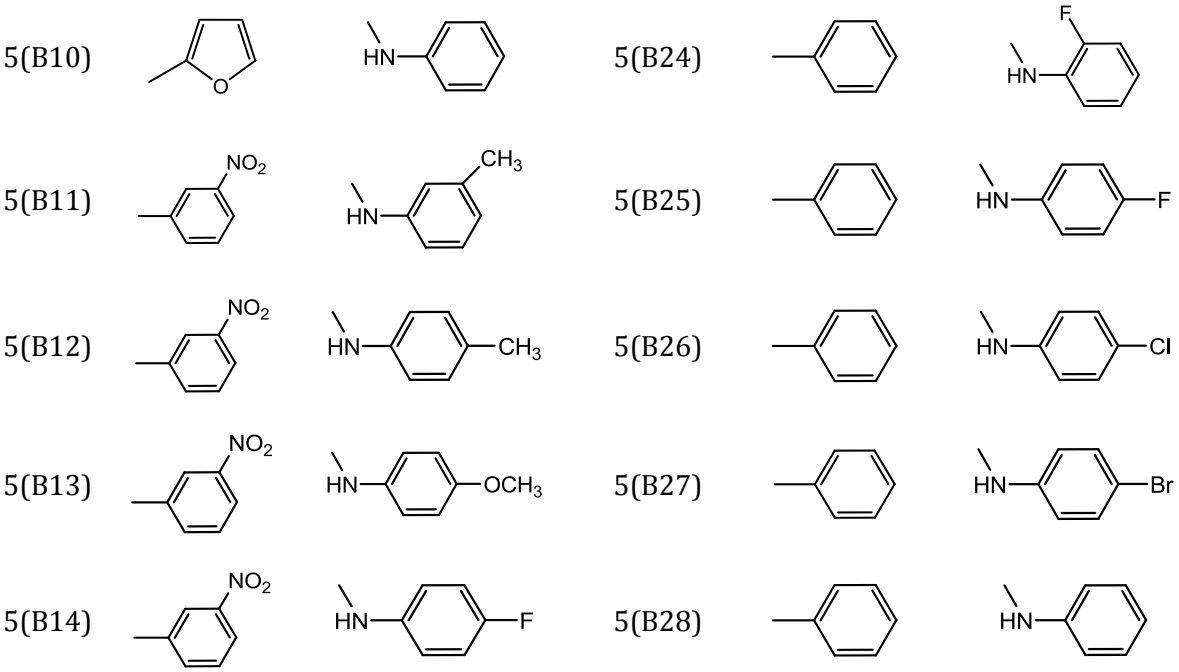


Figure 1: Rational for Designing of Subtitled Benzamide

Experimental

All the chemicals and reagents used were of laboratory grade and were purchased from E Merck Ltd., Loba Chemicals Ltd., Sigma-Aldrich Ltd. and Ranbaxy Chemicals Ltd.,India. The solvents used were dried and purified, as and when required. The melting points reported here in are uncorrected and were determined in open capillaries using the Thiele melting point apparatus. The reactions were monitored using TLC, which were performed on coated silica gel G plates.

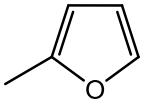
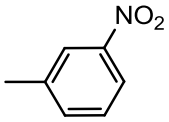
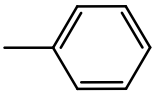
The plates were activated by heating (120ºC) for 30 minutes. They were developed using benzene:ethylacetate (1:0.1, A), benzene:ethylacetate (1:1, B), chloroform:methanol (1:0.1, C), benzene (D), benzene:ethylacetate (1:0.5, E) solvent system, and the spots were visualized by exposure to iodine vapors. IR spectra were recorded from KBr disks using a Shimadzu 8400-S FTIR, and elemental analyses were carried out using a FLASH EA-1112 CHN analyzer (Thermo Finnigan, Italy). The ^{1}H-NMR and ^{13}C NMR spectra of the synthesized compoundswere obtained using a Bruker DRX-300 (300MHz) NMR spectrometer. The chemical shifts obtained are reported in δ ppm. The mass spectra of the compounds were obtained using a JMS-T100LC, (Accu TOF) mass spectrometer (DART-MS), at the CDRI, Lucknow.

General procedure for synthesis of arylideneoxazolones 4(A1-A3) from benzoylglycine

A mixture of aromatic aldehydes (0.027 mol), benzoylglycine (0.027 mol), acetic anhydride (0.081 mol) and sodium acetate (0.027 mol) was heated in a 250 mL conical flask on an electric hotplate with constant shaking. As soon as the mixture liquefied

completely, it was transferred to a water bath and heated further for 2 hours. Then 50 mL of ethanol was added slowly to the contents of the flask, and the mixture was allowed to stand overnight, and a crystalline precipitate was obtained. The resultant product was filtered with suction, washed with ice-cold alcohol (2×10 mL) and then washed with boiling water (2×10 mL). It was dried at 100ºC and recrystallized to obtain arylideneoxazolones **4** (**A1-A3**), (**Table 1**).

Table 1: Physical properties of arylideneoxazolones 4(A1-A3)

Compound code	Ar	Molecular formula	Molecular weight	Melting range (°C)	Yield (%)
4(A1)		$C_{14}H_9NO_3$	239	171-173°C	78
4(A2)		$C_{16}H_{10}N_2O_4$	294	176-179°C	85
4(A3)		$C_{16}H_{11}NO_2$	249	165–1678C	61

4-(furan-2-ylmethylidene)-2-phenyl-1,3-oxazol-5(4H)-one 4(A1)

M.P.:171-173°C (78%, benzene, yellow crystalline); R_f 0.59 [benzene:ethyl acetate (4.9:0.1)];

IR (KBr) cm^{-1}: 3446(N-H), 3108(Ar C-H), 2990 (aliph. C-H) 1789(C=O), 1648(C=C), 1599(C=N); ^{1}H NMR: (CDCl3): δ (ppm) = 6.80-8.15 (9H, m, 8H arom + 1 olefinic CH); ^{13}C-NMR : (CDCl3): δ (ppm) = 166.23, 162.50, 151.65, 142.26, 131.57, 130.82, 128.93, 127.23, 126.09, 117.37, 114.76, 111.01; m/z- 239, 240(M+1), 241 (M+2); CHN calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86 Found C, 70.25; H, 3.83;N, 5.79.

4-(3-nitrobenzylidene)-2-phenyl-1, 3-oxazol-5(4H)-one 4(A2)

M.P.:176-179°C (85%, benzene, yellow crystalline); R_f 0.55 [benzene:ethyl acetate (4.9:0.1)];

IR (KBr) cm^{-1}: 3072(amine N-H), 3047(amide N-H), 2999(Ar C-H), 2920(aliph. C-H), 1657 (C=O), 1559(C=N), 1530 (C=C), 1450(NO_2), 1351 (C-H), 1167 (C-O-C), 1094(C-N); ^{1}H NMR: (CDCl3): δ (ppm) = 6.80-8.15 (9H, m, 8H arom. + 1 olefinic CH); ^{13}C-NMR: (CDCl3): δ (ppm) = 167.78, 163.56, 144.26, 132.78, 132.76, 131.57, 130.67, 130.25, 129.37, 128.93, 127.42, 127.23, 126.09; m/z- 294, 295(M+1), 296 (M+2); CHN calcd. for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52 Found C, 65.26; H, 3.39; N, 9.48.

4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-one 4(A3)

M.p.: 165–1678C (61%, benzene, yellow crystalline); R_f 0.62 [benzene:ethyl acetate (4.9:0.1)]; IR (KBr) cm^{-1} : 1793 (C=O),1647 (C=N), 1768 (C=C), 3068–3058 (Ar C–H), 3039 (aliph. C–H), 1296 (C–O).^{1}H-NMR: ($CDCl_3$): δ (ppm) ¼ 7.32–7.93 (11H, m, 10H arom. + 1 olefinic CH).^{13}C-NMR: (CDCl3): δ (ppm): 165.75, 160.85, 137.64, 129.17, 128.98, 128.51, 127.86, 127.49, 127.09, 126.67, 126.41, 113.74; m/z- 249, 250(M+1), 251 (M+2); CHN calcd. for $C_{16}H_{11}NO_2$: C, 77.1; H, 4.45;N, 5.62. Found: C, 77.05; H, 4.39; N, 5.52.

General procedure synthesis of benzamides 5(B1-B28)

Arylideneoxazolones 4(A1-A3, 0.002 mol) were suspended in 15 mL of dry toluene in a 50 mL round bottom flask (RBF). The appropriate amine (0.002 mol) was added to the contents of the RBF, and the reaction mixture was refluxed for about 30 minutes

to 4hours and allowed to cool overnight to obtain a solid precipitate. The resultant solid was collected by filtration and washed with 5 mL of 0.5 N HCl and then with water (2 × 5 mL). It was dried at 100ºC and recrystallized. Crystals of benzamides **5**(**B1-B28**), (**Table 2**) were obtained, the color being white to off-white.

Table 2: Physical properties of *N*-aminocarbonyl arylvinylbenzamides 5(B1-B28)

Compd. code	Molecular formula	Mol. Wt.	Melting range (°C)	Compd. code	Molecular formula	Mol. Wt.	Melting range (°C)
5(B1)	$C_{21}H_{18}N_2O_3$	346	175-178	5(B15)	$C_{22}H_{16}ClN_3O_4$	421	205-208
5(B2)	$C_{21}H_{18}N_2O_3$	346	190-193	5(B16)	$C_{22}H_{16}BrN_3O_4$	466	211-214
5(B3)	$C_{21}H_{18}N_2O_4$	362	147-149	5(B17)	$C_{22}H_{17}N_3O_4$	387	181-184
5(B4)	$C_{20}H_{15}N_3O_5$	377	212-214	5(B18)	$C_{19}H_{14}N_4O_4S$	394	198-201
5(B5)	$C_{20}H_{15}N_3O_5$	377	226-229	5(B19)	$C_{23}H_{20}N_2O_2$	356	234-236
5(B6)	$C_{20}H_{15}FN_2O_3$	350	165-168	5(B20)	$C_{23}H_{20}N_2O_2$	356	232-235
5(B7)	$C_{20}H_{15}FN_2O_3$	350	202-205	5(B21)	$C_{23}H_{20}N_2O_3$	372	193-196
5(B8)	$C_{20}H_{15}ClN_2O_3$	366	188-191	5(B22)	$C_{22}H_{17}N_3O_4$	387	141-143
5(B9)	$C_{20}H_{15}BrN_2O_3$	411	187-190	5(B23)	$C_{22}H_{17}N_3O_4$	387	146-148
5(B10)	$C_{20}H_{16}N_2O_3$	332	205-207	5(B24)	$C_{22}H_{17}FN_2O_2$	360	162-165
5(B11)	$C_{23}H_{19}N_3O_4$	401	218-221	5(B25)	$C_{22}H_{17}FN_2O_2$	360	254-257
5(B12)	$C_{23}H_{19}N_3O_4$	401	195-198	5(B26)	$C_{22}H_{17}ClN_2O_2$	377	244-247
5(B13)	$C_{23}H_{19}N_3O_5$	417	231-234	5(B27)	$C_{22}H_{17}BrN_2O_2$	421	211-213
5(B14)	$C_{22}H_{16}FN_3O_4$	405	224-227	5(B28)	$C_{22}H_{18}N_2O_2$	342	238-241

***N*-{1-(furan-2-yl)-3-[(3-methylphenyl) amino]-3-oxoprop-1-en-2-yl}benzamide 5(B1)**

M.P. : 175-178°C (89%, ethanol, white crystalline); IR (KBr) cm^{-1}: 3252(Amine -NH), 3143 (amide -NH), 2921(Ar C-H), 2859 (aliph C-H), 1644(C=O),1553(N-H),1463 (C-H),1294(C-O-C), 1263(C-N),1207(C-C); ^{1}H NMR: (DMSO-d6): δ (ppm)= 9.94,9.95(2H, s, amide -NH), 6.60-8.07(13H, m, 12 arom. H + 1 olefinic H), 2.28 (3H, s, $-CH_3$); ^{13}C NMR: (DMSO-d6): δ (ppm) = 165.65, 163.36, 149.71, 144.57, 139.02, 137.58, 133.66, 131.70, 128.34, 127.90, 124.13, 120.73, 117.40, 116.96, 114.04, 112.28, 21.14; M.S.: m/z- 346, 347(M+1), 241, 137, 107; CHN calcd. For $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09 Found: C, 72.68; H, 4.99; N, 7.98.

***N*-{1-(furan-2-yl)-3-[(4-methylphenyl) amino]-3-oxoprop-1-en-2-yl}benzamide 5(B2)**

M.P. : 190-193 °C (87%, benzene, yellow crystalline); IR (KBr) cm^{-1}: 3196(Amine N-H), 3119(amide N-H), 2919(Ar C-H), 2863(aliph C-H), 1637(C=O), 1576(N-H), 1483(C-H), 1288(C-O-C), 1207(C-N), 1146(C-C); ^{1}H NMR: (DMSO-d6): δ (ppm) = 9.92, 9.95 (2H, s, amide -NH), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 2.26 (3H, s, $-CH_3$); ^{13}C NMR: (DMSO-d6): δ (ppm) = 165.65, 163.28, 149.76, 144.60, 136.62, 133.69, 132.39, 131.74,1 28.88, 128.38, 127.94, 120.26, 116.99, 114.06, 112.32, 20.50; M.S.: m/z- 346, 347(M+1), 241, 137, 107; CHN calcd. For $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09 Found: C, 72.70; H, 5.09; N, 8.01.

***N*-{1-(furan-2-yl)-3-[(4-methoxyphenyl) amino]-3-oxoprop-1-en-2-yl}benzamide 5(B3)**

M.P.: 147-149 °C (73%, ethanol, off white crystalline); IR (KBr) cm^{-1}: 3245(Amine N-H), 3127(amide N-H), 3064(Ar C-H), 3001 (aliph C-H), 1650(C=O), 1510(N-H), 1441 (C-H), 1245(C-O-C), 1234(C-N), 1174 (C-C); ^{1}H NMR: (DMSO-d6): δ (ppm) = 9.91, 9.93 (2H, s, amide-NH), 6.60-8.07 (13H, m, 12 arom. H + 1 olefinic H), 3.73 (3H, s, $-OCH_3$); ^{13}C NMR: (DMSO-d6): δ (ppm) = 163.04, 155.41, 149.77, 144.51, 133.73, 132.17, 131.67, 128.88, 128.33, 127.91, 121.84, 116.95, 113.94, 113.59, 112.27, 55.15; M.S.: m/z- 362, 363(M+1), 241, 137, 123; CHN

calcd. For $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73 Found: C, 69.23; H, 4.98; N, 7.22.

N-{1-(furan-2-yl)-3-[(3-nitrophenyl) amino]-3-oxoprop-1-en-2-yl}Benzamide 5(B4)

M.P.:212-214°C (71%, benzene, white crystalline); IR (KBr) cm^{-1}: 3296(Amine N-H), 3125(amide N-H), 2919(Ar C-H), 2849 (aliph C-H), 1659(C=O), 1512 (N-H), 1528(NO_2), 1462 (C-H), 1286(C-O-C), 1248(C-N), 1206(C-C); ^1H NMR: (DMSO-d6): δ (ppm) = 10.04, 10.52 (2H, s, amide -NH), 6.63-8.72 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =149.54, 144.93, 131.81, 129.95, 128.39, 127.91, 126.06, 119.43, 117.91, 117.48, 114.67, 114.21, 112.39; M.S.: m/z- 377,378(M+1), 241,137,138; CHN calcd. For $C_{20}H_{15}N_3O_5$: C, 63.66; H, 4.01; N, 11.14 Found: C, 62.58; H, 3.95; N, 11.02.

N-{1-(furan-2-yl)-3-[(4-nitrophenyl) amino]-3-oxoprop-1-en-2-yl}benzamide 5(B5)

M.P.: 226-229°C (78%, ethanol, yellow crystalline); IR (KBr) cm^{-1}: 3291(Amine N-H), 3143(amide N-H), 3110(Ar C-H), 3064 (aliph C-H), 1654(C=O), 1598(N-H), 1555(NO_2), 1464 (C-H), 1297(C-O-C), 1233(C-N), 1204(C-C); ^1H NMR: (DMSO-d6): δ (ppm) = 10.67, 10.05 (2H, s, amide-NH), 6.64-8.26 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) = 149.49, 148.08, 129.34, 128.44, 127.91, 127.32, 124.75, 119.67; M.S.: m/z- 377, 378 (M+1), 241,137,138; CHN calcd. For $C_{20}H_{15}N_3O_5$: C, 63.66; H, 4.01; N, 11.14 Found: C, 63.53; H, 3.99; N, 10.97.

N-[3-[(2-fluorophenyl)amino]-1-(furan-2-yl)-3-oxoprop-1-en-2-yl]benzamide 5(B6)

M.P.:165-168°C (61%, ethanol, faint brown crystalline); IR (KBr) cm^{-1}: 3274(Amine N-H), 3122(amide N-H), 3055(Ar C-H), 2933(aliph C-H), 1650(C=O), 1599, 1531(N-H), 1479 (C-H), 1260(C-O-C), 1196(C-N), 1113(C-C), 1020(C-F); ^1H NMR: (DMSO-d6): δ (ppm) = 9.69, 9.99 (2H, s, amide -NH), 6.61-8.07 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =165.89, 163.33, 149.57, 144.90, 133.65, 131.69, 128.32, 127.83, 126.76, 126.19, 125.75, 124.18, 118.40, 115.64, 114.68, 112.30, 99.46; M.S.: m/z- 350,351(M+1), 241,137,111; CHN calcd. For $C_{20}H_{15}FN_2O_3$: C, 68.57; H, 4.32; N, 8.00 Found: C, 68.10; H, 4.21; N, 7.98.

N-[3-[(4-fluorophenyl)amino]-1-(furan-2-yl)-3-oxoprop-1-en-2-yl]benzamide 5(B7)

M.P.:202-205°C (63%, ethanol, colorless crystalline); IR (KBr) cm^{-1}: 3227(Amine N-H), 3150(amide N-H), 3061 (Ar C-H), 3032(aliph C-H), 1640(C=O), 1569, 1509(N-H), 1410 (C-H), 1263(C-O-C), 1211(C-N), 1158(C-C), 1018 (C-F); ^1H NMR: (DMSO-d6): δ (ppm) = 9.96, 10.11 (2H, s, amide-NH), 6.61-8.07 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =149.64, 144.56, 133.62, 131.66, 128.29, 127.85, 122.06, 121.96, 116.95, 115.11, 114.82, 114.08, 112.23; M.S.: m/z-350,351(M+1), 241,137,111; CHN calcd. For $C_{20}H_{15}FN_2O_3$: C, 68.57; H, 4.32; N, 8.00 Found: C, 68.21; H, 4.22; N, 7.95.

N-[3-[(4-chlorophenyl)amino]-1-(furan-2-yl)-3-oxoprop-1-en-2-yl]benzamide 5(B8)

M.P.:188-191°C (67%, ethanol, white crystalline); IR (KBr) cm^{-1}: 3245(Amine N-H), 3186(amide N-H), 3112 (Ar C-H), 3056(aliph C-H), 1660(C=O), 1515(N-H), 1465 (C-H), 1289(C-O-C), 1253(C-N), 1151(C-C), 742 (Cl); ^1H NMR: (DMSO-d6): δ (ppm) = 9.97, 10.19 (2H, s, amide-NH), 6.61-8.07 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =165.68, 163.63, 149.64, 144.73, 138.14, 133.57, 131.78, 128.39, 127.92, 127.72, 127.04, 121.73, 117.09, 114.31, 112.34; M.S.: m/z-366, 367(M+1), 331, 241,137,127; CHN calcd. For $C_{20}H_{15}ClN_2O_3$: C, 65.49; H, 4.14; N, 7.64 Found: C, 65.37; H, 4.01; N, 7.01.

N-[3-[(4-bromophenyl)amino]-1-(furan-2-yl)-3-oxoprop-1-en-2-yl]benzamide 5(B9)

M.P.:187-190°C (59%, ethanol, blackish crystalline); IR (KBr) cm^{-1}: 3276(Amine N-H), 3185(amide N-H), 3106 (Ar C-H), 3057(aliph C-H), 1670(C=O), 1596(C=C), 1562(N-H), 1457 (C-H), 1282(C-O-C), 1242(C-N), 1149(C-C), 701(C-Br); ^1H NMR: (DMSO-d6): δ (ppm) = 9.97, 10.18 (2H, s, amide-NH), 6.61-8.07 (13H, m, 12 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =163.65, 149.64, 144.77, 138.59, 133.56, 131.79, 131.32 128.40, 127.93, 127.73, 122.10, 117.11, 114.35, 112.36; M.S.: m/z-411, 412(M+1), 241,137,172; CHN calcd. For $C_{20}H_{15}BrN_2O_3$: C, 58.41; H, 3.68; N, 6.81 Found: C, 57.93; H, 3.12; N, 6.79.

N-[3-oxo-1-phenyl-3-(phenylamino)prop-1-en-2-yl]benzamide 5(B10)

M.P.:205-207°C (85%, ethanol, faint yellowish crystalline); IR (KBr) cm^{-1}: 3275(Amine N-H), 3197(amide N-H), 3142(Ar C-H), 3064(aliph C-H), 1651(C=O), 1545(C=C), 1512(N-H), 1465 (C-H), 1288(C-O-C), 1209(C-N), 1146(C-C); ^1H NMR: (DMSO-d6): δ (ppm) = 9.95, 10.05 (2H, s, amide-NH), 6.61-8.08 (14H, m, 13 arom. H + 1 olefinic H); ^{13}C NMR: (DMSO-d6): δ (ppm) =165.63, 163.43, 149.68, 144.53, 139.08, 133.64, 131.66, 128.41, 128.31, 127.86, 123.41, 120.21, 116.91, 114.03, 112.24, 99.46; M.S.: m/z- 332, 333(M+1), 241,137, 93; CHN calcd. For $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43 Found: C, 72.02; H, 4.71; N, 8.39.

N-[3-[(3-methylphenyl)amino]-1-(3-nitro-phenyl)-3-oxoprop-1-en-2-yl]benzamide 5(B11)

M.P.:218-221°C (88%, benzene, white crystalline); IR (KBr) cm^{-1}: 3236(Amine N-H), 3191(amide N-H), 2981(Ar C-H), 2919(aliph C-H), 1648(C=O), 1525(NO_2), 1476(N-H), 1443(C-H),1 291(C-O-C), 1257(C-N),1177(C-C); ^1H NMR: (DMSO-d6): δ (ppm) = 10.21, 10.27(2H, s, amide-NH), 6.69-8.53 (14H, m, 13 arom. H + 1 olefinic H), 2.30 (3H, s, $-CH_3$); ^{13}C NMR: (DMSO-d6): δ (ppm) = 163.72, 147.77, 137.63, 136.16, 135.70, 133.30, 131.85, 129.97, 128.32, 127.81, 125.17, 124.19, 123.36, 122.80, 120.55, 117.23, 21.12; M.S.: m/z- 401, 402(M+1), 296, 192,107; CHN calcd. For $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47 Found: C, 68.67; H, 4.37; N, 10.13.

Similarly, structures of all other benzamide derivatives are characterized by spectral method, IR, NMR, Mass.

Biological Activity

The synthesized compounds **5**(**B1-B28**) were screened for activity against *Aspergillus niger* (NCIM 545)*, Penicillium chrysogenum* (NCIM 709), and *Candida albicans* (NCIM 3471) in DMSO using the disk diffusion method [25]. Potato dextrose agar was prepared by dissolving peptone (0.05g), yeast extract (0.3 g), glucose (1.0 g) and malt extract (0.3 g) in distilled water (100 mL) and adjusting the pH to 6.4. Normal saline was used to make a suspension of fungal spores for lawning. A loopful of a particular fungal strain was transferred to 3 mL of saline to get a suspension of the corresponding species. Twenty milliliters of agar media was poured into empty, sterile petri dish. The excess suspension was decanted, and the plates maintained in an incubator at 37ºC for 1 hour for drying. Agar disks were made using these seeded agar plates, and 10 μg/mL of a test compound in DMSO was added to each disk. A control was also prepared in the same way, using the DMSO solvent. The petri-dishes were prepared in triplicate and maintained at 37ºC for 4 days. The activity of each compound was compared with that of ketoconazole, which was used as a standard.

The minimum inhibitory concentration (MIC) values were determined for those fungi that were sensitive to the compounds in the disk diffusion assay The MIC is defined for our purpose as the lowest concentration of a compound with which there was no visible fungal growth after incubation. The broth dilution method was used to determine the MIC values. The procedure followed was as described in the literature [25]. The compounds were prepared at the highest concentration (1mg/mL) and serial two-fold dilutions were made to obtain concentrations ranging from 0.06 to 1054 μg/mL.

Docking Study

The degree to which the synthesized novel molecules will affect their target in terms of structural and chemical complementation was explored using the Glide 4.5 [26,27] module of the Schrödinger molecular modeling interface. Glide searches for favorable interactions between one or more ligand molecules and a receptor molecule using a grid-based method.

For the present study, the X-ray crystal structure of the twinned 1.9 Å structure of sterol 14α-demethylase complexed with *N*-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide (PDB entry: 3GW9) was taken from PDB (www.rscb.org). Before docking, the proteins were prepared using the protein preparation wizard [28]: removing the water molecule and cofactors from the proteins, optimizing hydrogen bonding and deleting the ligand present in the crystal

structure. The solvent molecules were deleted, and the bond order of the crystal ligand and protein was adjusted. The structures were minimized up to 0.30 Å RMSD. The ligands were built using the build panel of Maestro 8.0, [29] build pannel and prepared using LigPrep 2.1 [30] and the OPLS-2005 force field [30]. Using the extra precision (XP) mode of Glide 4.5, all the molecules were docked into the active site of a target molecule, and final scoring was carried out in terms of the Glide multi-ligand scoring function.

Drug Likeness (Lipinski's Rule of Five)

As a part of our study, the compliance of compounds to Lipinski's rule of five was evaluated. As discussed by Lipinski, molecular properties are closely related to the oral bioavailability of a drug. Although the cytotoxic effects of lead compounds are thought to be primarily due to their ability to modulate cell death, other factors such as solubility, stability and/or efflux properties within the cell may also contribute. The QikProp 3.2 was used to analyze drug likeness (Lipinski's Rule of Five).

RESULTS AND DISCUSSION

The physical properties of all the synthesized compounds were characterized, and their spectral data were obtained. The purity and homogeneity of the compounds were confirmed using single-spot thin-layer chromatography (TLC). Spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry) of the compounds confirmed the structures of the synthesized compounds. The IR spectrum of B4 contains broadened N-H bands indicating the presence of amide fragments, between 3125 and 3296 cm^{-1}. Strong C=O bands are found at 1640 -1680 cm^{-1}, a strong NO_2 band is observed at 1528 cm^{-1}, and the characteristic C-N and C-O stretching are seen in the area of 1240-1295 cm^{-1}. In the ^{1}H NMR spectra of compound **5**(**B4**), the protons of the amide group are observed as a broad singlet at 10.4-10.52 ppm and the remaining 13 aromatic protons showed mutilate at 6.63-8.72 ppm. The ^{13}C NMR spectra show a chemical shift at 112.39-149.54, which is due to the presence of olefinic -CH_2. The mass spectral data of all the synthesized compounds are in accordance with their proposed molecular weights.

Table 3: Antifungal screening of the *N*-aminocarbonyl arylvinyl benzamides 5(B1-B28), Minimum Inhibitory Cocentration (MIC), µg/ml

Compd.	*C.a.*	*A.n.*	*P.C.*	Compd.	*C.a.*	*A.n.*	*P.C.*
5(B1)	16	32	8	5(B15)	8	8	8
5(B2)	16	32	8	5(B16)	32	16	16
5(B3)	16	8	8	5(B17)	8	32	32
5(B4)	2	4	2	5(B18)	16	8	8
5(B5)	8	16	8	5(B19)	8	8	8
5(B6)	2	2	4	5(B20)	8	16	8
5(B7)	8	16	8	5(B21)	8	8	8
5(B8)	8	8	8	5(B22)	2	2	2
5(B9)	8	8	16	5(B23)	8	8	16
5(B10)	32	32	16	5(B24)	16	8	8
5(B11)	8	8	8	5(B25)	16	8	8
5(B12)	8	8	16	5(B26)	8	16	8
5(B13)	8	8	8	5(B27)	16	8	8
5(B14)	16	8	8	5(B28)	8	8	8
Ketoconazole	0.25	0.25	0.25	Ketoconazole	0.25	0.25	0.25

C.a.* =Candida albicans*; ***A.n.* =** *Aspergillus niger*; ***P.c.*=** *Penicillium chrysogenum*;

Table 4: Docking results of *N*-aminocarbonyl arylvinylbenzamides 5(B1-B28)

Compound code	Glide gscore	Glide lipophilic	Glide energy	Compound code	Glide gscore	Glide lipophilic	Glide energy
5(B22)	-8.74	-4.95	-52.49	5(B13)	-6.85	-2.13	-55.44
5(B6)	-8.65	-4.57	-46.27	5(B26)	-6.84	-2.29	-50.5
5(B4)	-8.61	-4.76	-45.32	5(B23)	-6.81	-2.27	-51.37
5(B21)	-8.27	-3.96	-40.47	5(B5)	-6.81	-2.390	-42.35
5(B27)	-7.95	-4.49	-47.39	5(B19)	-6.73	-2.280	-48.99
5(B9)	-7.92	-4.80	-35.30	5(B18)	-6.64	-2.00	-51.64
5(B15)	-7.87	-4.70	-37.79	5(B20)	-6.62	-2.20	-49.02
5(B11)	-7.73	-4.71	-37.37	5(B8)	-6.54	-2.58	-40.46
5(B12)	-7.65	-3.66	-48.41	5(B24)	-6.23	-3.15	-37.76
5(B28)	-7.24	-3.85	-41.39	5(B2)	-6.09	-2.37	-49.47
5(B17)	-7.01	-3.50	-43.97	5(B1)	-6.04	-3.44	-36.77
5(B14)	-6.94	-2.21	-52.72	5(B7)	-5.76	-3.09	-38.66
5(B25)	-6.91	-3.86	-38.31	5(B3)	-5.21	-1.63	-45.03
5(B11)	-6.87	-2.23	-54.47	5(B16)	-4.23	-1.76	-42.92

Antifungal Activity

The antifungal activity of the novel *N*-aminocarbonyl arylvinylbenzamides against fungal strains (*Candida albicans, Aspergillus niger* and *Penicillium chysogenum*) is summarized in **Table 3**. Compound 5(**B22**) shows much better inhibition of growth of *Candida albicans, Aspergillus niger* and *Penicillium chyrsogenum*, compared with **5**(**B1-B28**).

Structure-activity relationship (SAR) and docking study

Regarding the structure–activity relationship of the novel *N*-aminocarbonyl arylvinylbenzamides derivatives **5**(**B1-B28**) showed better antifungal activity against the tested fungal strain. The results reveal that the new compound 5(**B22**) contain benzylidene nucleus with the electron-withdrawing nitro group on the aminocarbonyl phenyl ring, which exhibits a broad-spectrum antifungal profile compared to 5(**B6**), contained furylidine nucleus with the electron-with drawing fluro group on aminocarbonyl phenyl ring. Also compound **5**(**B4**), having electron withdrawing nitro group, on aminocarbonyl phenyl ring, were found to produce comparable activity with that of **5**(**B22**) and **5**(**B6**).

Electron-withdrawing chloro group of nitrobenzylidine nucleus give rise less powerful antifungal activity compared with **5**(**B22**), **5**(**B4**) and **5**(**B6**) against *Penicillium chrysogenum,* and the electron-withdrawing groups on benzimidazole, benzoxazole and benzothiazole do not affect the growth-inhibitory activity against the fungal strains tested. Furthermore, methoxy benzylidine and 3-nitro benzylidine were found to show moderate antifungal activity. In general, most of the compounds tested displayed better activity against the fungal strains (*Candida albicans, Aspergillus niger* and *Penicillium chrysogenum*). It should also be noted that benzimidazole derivatives have better antibacterial potential and benzothiazole derivatives have better antifungal potential.

Docking Study

All the synthesized compounds were subjected to grid-based molecular docking studies. The results show that compounds **5**(**B22**), **5**(**B6**), **5**(**B4**), **5**(**B21**), **5**(**B9**), **5**(**B11**), and **5**(**B15**) had a better Glide score (Gscore) compared with respect to the crystal structure of sterol 14α-demethylase (**Table 4**).

Binding mode of **5**(**B22**), **5**(**B6**), **5**(**B21**), and inactive compound **5**(**B16**) in the X-ray crystal structure of 14α-demethylase complexed with *N*-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide (PDB entry: 3GW9) is shown in **Figure 2**. Compound **5**(**B22**) shows hydrogen bond interaction with TYR103, TYR116 and ARG361; Compound **5**(**B6**) with TYR103, TYR116 and Compound **5**(**B21**) with MET160, MET358; on the other hand

Compound **5**(**B16**) is not showing any kind of hydrogen bonding interaction; may be the reason for its lower antifungal activity.

5.4 Drug Likeness (Lipinski's Rule of Five)

The QikProp 3.2 was used to analyze drug likeness (Lipinski's Rule of Five); the results are given in **Table 5**. It was found that all the synthesized compounds comply with these rules. All the Lipinski's parameters are within the acceptable range, thereby indicating their potential as a drug-like molecule.

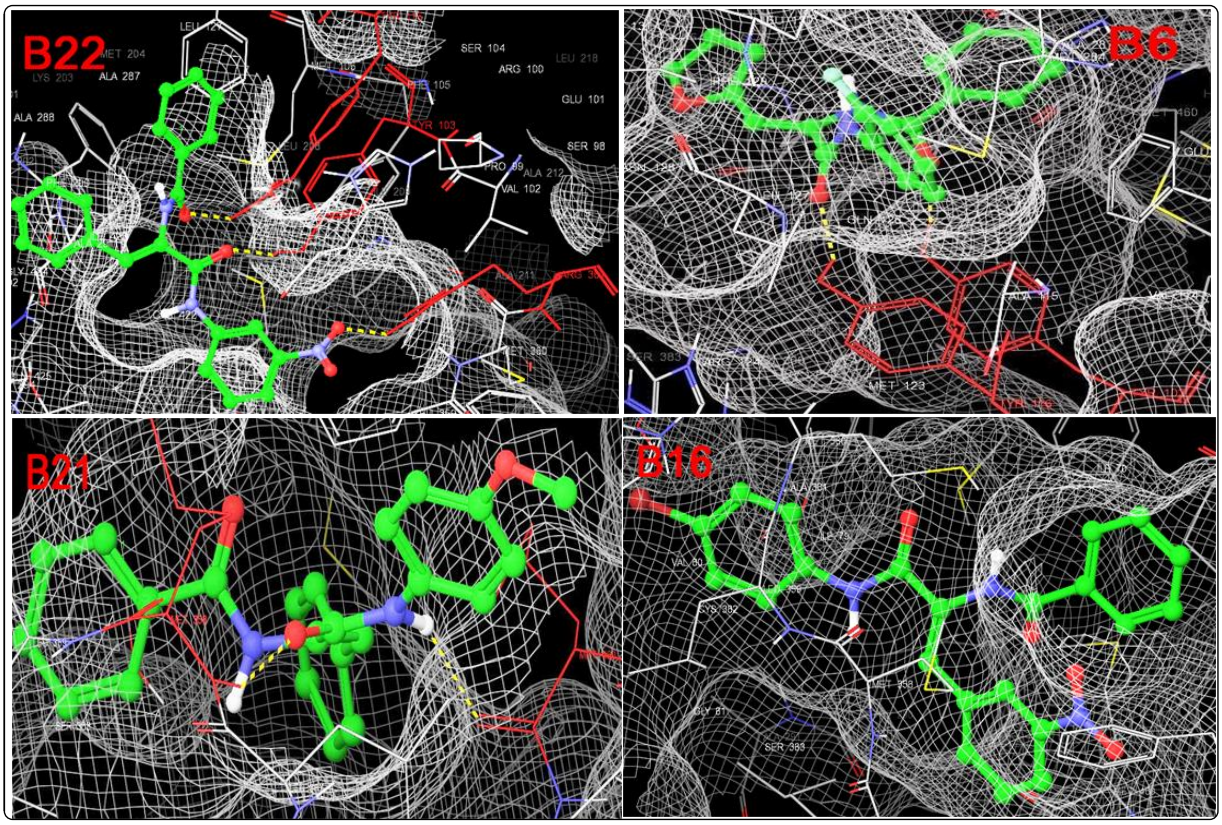


Figure 2: Binding mode of 5(**B22), 5(B6),5(B21),** and inactive compound **5(B16)** in the X-ray crystal structure of 14α-demethylase complexed with *N*-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadi-azol-2-yl)benzamide (PDB entry: *3GW9).* Compound 5(**B22)** shows hydrogen bond interaction with TYR103,TYR116 and ARG361; Compound 5(**B6)** with TYR103,TYR116 and Compound **5(B21)** with MET160, MET358; on the other hand Compound 5(**B16)** is not showing any kind of hydrogen bonding interaction; may be the reason for its least activity.

CONCLUSION

A total of **28** compounds were synthesized and screened for antifungal activity against *Candida albicans , Aspergillus niger,*and *Penicillium chrysogenum*. Among the compounds tested and **5**(**B4**), **5**(**B6**), **5**(**B9**), **5**(**B11**), **5**(**B15**) **5**(**B21**), and **5**(**B22**), displayed significant antifungal activity, while all other the benzamide derivatives showed moderate antifungal activity compared with the standards. In addition, the binding mode of the tested compounds inside the sterol 14α-demethylase active site was predicted using a docking technique. The data obtained showed an orientation of the synthesized derivatives in the sterol 14α-demethylase active site that is similar to that in the reported data regarding for similar sterol 14α-demethylase inhibitors.

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Table 5: Lipinski's parameter data for *N*-aminocarbonyl arylvinylbenzamides 5(B1-B28)

Compound code	Molecular Weight	Hydrogen Bond Donnor	Hydrogen Bond Acceptor	Q P logPo/w	Rule of Five	Compound Code	Molecular Weight	Hydrogen Bond Donnor	Hydrogen Bond Acceptor	Q P logPo/w	Rule of Five
5(B1)	346.385	1.25	4.75	4.482	0	5(B15)	421.839	1.25	5.25	4.702	0
5(B2)	346.385	1.25	4.75	4.482	0	5(B16)	466.29	1.25	5.25	4.641	0
5(B3)	362.384	1.25	5.5	4.271	0	5(B17)	387.394	1.25	5.25	4.071	0
5(B4)	377.356	1.25	5.75	3.474	0	5(B18)	394.404	1.25	6.75	3.34	0
5(B5)	377.356	1.25	5.75	3.47	0	5(B19)	356.423	1.25	4.25	4.084	0
5(B6)	350.348	1.25	4.75	4.367	0	5(B20)	356.423	1.25	4.25	4.083	0
5(B7)	350.348	1.25	4.75	4.41	0	5(B21)	372.423	1.25	5	4.871	0
5(B8)	366.803	1.25	4.75	4.666	0	5(B22)	387.394	1.25	4.25	4.073	0
5(B9)	411.254	1.25	4.75	4.743	0	5(B23)	387.394	1.25	5.25	4.067	0
5(B10)	332.358	1.25	4.75	4.175	0	5(B24)	360.387	1.25	4.25	4.968	0
5(B11)	401.421	1.25	5.25	4.383	0	5(B25)	360.387	1.25	4.25	4.009	0
5(B12)	401.421	1.25	5.25	4.379	0	5(B26)	376.841	1.25	4.25	4.267	0
5(B13)	417.42	1.25	6	4.164	0	5(B27)	421.292	1.25	4.25	4.344	0
5(B14)	405.384	1.25	5.25	4.444	0	5(B28)	342.396	1.25	4.25	4.773	0

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