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DESIGN AND SYNTHESIS OF NOVEL 2-(4-((5-PHENYL-1, 3, 4-OXADIAZOL-2-YL)METHOXY)SUBSTITUTEDPHENYL)-1*H*-BENZO [de]ISOQUINOLINE-1, 3(2*H*)-DIONE DERIVATIVE AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS

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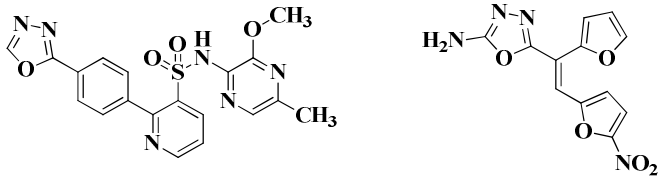
Abstract: A new series of 2-(4-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione derivatives **(6a-l)** have been synthesized by using conventional method. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activity against gram positive bacteria *S. aureus* gram negative bacteria *E. coli* and ciprofloxacin used standard drug. The antifungal activity screened against two pathogenic fungal strains *A.niger* and *C. albicans* and *Voriconazole* used as standard drug. The antibacterial results shows that compounds **6i** more than **6f** are as potent against *S. aureus* with compare to standard drug. In the case of *B. subtilis* the compounds **6f** more than **6i** are more active. In the case of *E.coli* the compounds **6i** more than **6f** are more active. The compounds **6f** and **6i** are more active against *P. aeruginosa*. The anti-fungal activity result shows that the compounds **6f** and **6i** are as active as standard drug Voriconazole against *A.niger*. In the case of *C. albicans* the compounds **6f** and **6i** are showing the same activity with compare to standard drug. All the synthesized novel compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, HRMS spectroscopic methods and the elemental analysis (C, H and N).

Key words: 2-(4-hydroxyphenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione, 1,8-Naphthalic anhydride, antibacterial activity, antifungal activity.

Introduction

Cyclic Imides are important class of compounds in the construction of macromolecules,[1, 2] as well as supramolecular assembly.[3-9] They are useful fluoroprobes for various studies,[10-14] and also serve as precursors for protection of the amine group.[15-19] Naphthalimides are important aromatic heterocycles with immense pharmacological significance as they serve as core scaffold for many antitumor, anti-inflammatory, antidepressant, antiprotozoal and antiviral agents, etc. The tricyclic planar ring system of naphthalimide is primarily responsible for its intercalation with DNA to perturb the cellular events and the substitution pattern of the

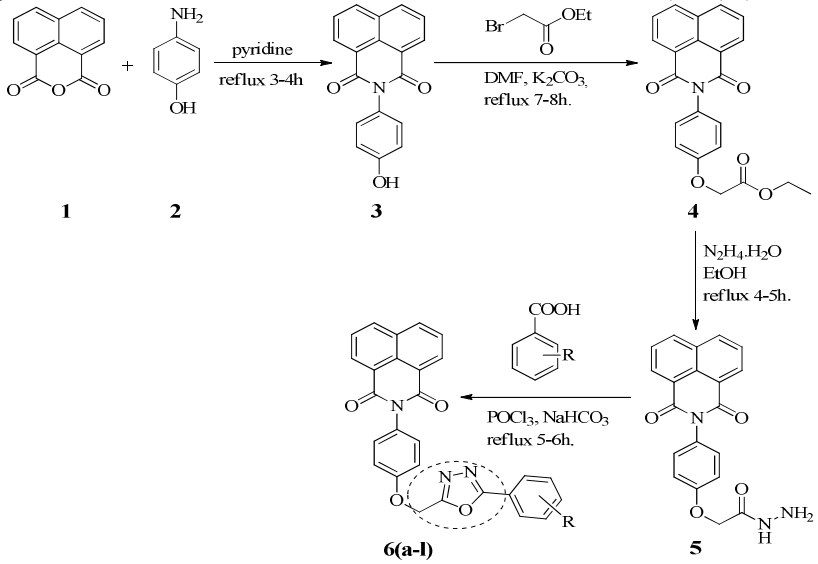
molecule leads to several other applications. The promising pharmacological activity profile and ease of synthesis have been attractive in design and development of new class of naphthalimides and their conjugates as various potential therapeutic agents. Few of such molecules are currently under preclinical and clinical evaluations.[20] They have also been shown to demonstrate potent anti-cancer activity, particularly active against a variety of murine and human cancer cell lines.[21] An example of this is Amonafide, a 3-aminonaphthalimide structure developed as a topoisomerase-II inhibitor, which displays potent activity against acute myeloid leukemia (AML).[22] On the other hand the heterocyclic nucleus 1,3,4-oxadiazole constitutes an important class of compounds for new drug development. In recent decades, the synthesis of 1, 3, 4-oxadiazole derivatives and their chemical and biological behavior have gained more importance. Oxadiazole compounds possess an extensive spectrum of pharmacological activities. In particular, compounds bearing 1,3,4-oxadiazole nucleus are known to exhibit unique anti-inflammatory, analgesic, antimicrobial, antitumor, anticonvulsant, anthelmintic, anti-mycobacterial, herbicidal, antioxidant and antiviral activities.[23] Some of the biologically active amino1, 3, 4-oxadiazole drugs are shown in **Fig.1**



Zibotentan **Furamizole**

Fig. 1 Structure of the medicinally important substituted amino1, 3, 4-oxadiazoles

In this communication we report the synthesis and antimicrobial and antifungal activities of novel 1,8-naphthalimide substituted-1, 3, 4-oxadiazoles derivatives **(6a-l)** (**scheme-1**).



Scheme1. Synthesis of novel 2-(4-((5-phenyl-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione derivatives in the presence of $POCl_3$

Material and methods

General methods

Melting points were determined on open capillaries using a cintex melting point apparatus. T.L.C analyses were performed on pre-coated silica gel (E-Merck Kieselgel 60F254) plates

and visualization was done by exposing to iodine vapor. Solvents were purified by standard procedures before use. IR Spectra were recorded in KBr on Perkin-Elmer Spectrum BX series FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on DRX 500MHz Bruker spectrometers using TMS as internal standard (chemical shifts are given in δ ppm). Mass spectra were recorded on a Varian MATCH-7 at 70ev. Elemental analyses were carried out on a carloerba 106 and Perkin-Elmer Analyzer. All the chemicals used in the present investigation were purchased from Sigma-Aldrich, India and used as such.

Synthesis of 2-(4-hydroxyphenyl)-1*H*-benzo [de]isoquinoline-1,3(2*H*)-dione (3)

A mixture of 1, 8-naphthalic anhydride (0.01mmol), 4-aminophenol (0.02mmol) was charged in RBF equipped with reflux condenser, to this mixture 2 mL of methanol was added, the resultant mixture was stirred at 70^{o}C for 3-4h. The progress of the reaction was monitored by TLC. After the completion of the reaction as indicated by TLC the reaction mixture was allowed to cool at room temperature. The precipitate formed was filtered off and the products were recrystallized with ether to give the compound (**3**). Yield: (80%). Brown powder; M.P = 119-120^{0}C; IR (KBr) (νmax, cm^{-1}): 3313; 1647; 1188; ^{1}H-NMR (500 MHz, DMSO) δ = 8.56 - 8.32 (m, 4H), 7.92 - 7.89 (d, *J* = 7.6 Hz 2H), 7.14-7.24 (d, *J* = 11.9 Hz, 2H), 7.01-6.87 (d, *J* = 11.9 Hz, 2H), 5.21-5.41 (s, 1H); ^{13}C-NMR (126 MHz, DMSO) δ 160.35 (s), 154.59 (s), 138.19 (s), 137.19 (s), 137.79 (s), 130.39 (s), 129.26 (s), 126.70 (s), 125.88 (s), 125.07 (s), 116.86 (s): HRMS (ESI): 289.170; Elemental Analysis calculated for $C_{18}H_{11}NO_3$, C, 74.73; H, 3.83; N, 4.84; found C, 74.77; H, 3.93; N, 4.88%.

Synthesis of ethyl 2-(4-(1,3-dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)phenoxy)acetate (4)

A mixture of 2-(4-hydroxyphenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (**3**) (0.02M) anhydrous K_2CO_3 (0.03M), Ethylbromoacetate (0.02M) and dimethyl formamide was stirred at room temperature for 8h. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as eluent. The reaction mixture was diluted with ice-cold water. The separated solid was filtered off and dried to afford the compound (**4**). Yield: (75%). yellow powder; M.P: 108-110^{0}C; IR (KBr) (νmax, cm^{-1}): 3413; 1659; 1190; 1367; 1390; 1140; ^{1}H-NMR (500 MHz, $CDCl_3$) δ=8.51-7.56 (m, 4H),7.92 -7.63 (t, 2H), 7.24-7.14 (d, *J* = 11.9 Hz, 2H), 7.04- 6.86 (d, *J* = 15.5, 7.9 Hz, 2H), 5.27 - 4.81 (s, 2H), 4.52 -3.65 (qrt, *J* = 5.7 Hz, 2H), 1.58- 1.19 (t, 3H): ^{13}C-NMR (126 MHz, $CDCl_3$) δ 169.70 (s), 157.93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 129.83 (d, *J* = 3.6 Hz), 126.16 (s), 124.53 (d, *J* = 29.0 Hz), 127.56 (s), 65.54 (s), 62.00 (s), 14.80 (s): HRMS (ESI): 376.210; Elemental Analysis calculated for $C_{22}H_{17}NO_5$,C, 70.39; H, 4.56; N, 3.73; found C, 70.59; H, 4.58; N, 3.76%.

Synthesis of 2-(4-(1,3-dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)phenoxy)acetohydrazide(5)

A mixture of ethyl 2-(4-(1,3-dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)phenoxy)acetate (**4**) (0.01mmol) and hydrazine hydrate (0.015mmol) in ethanol 20 mL was refluxed for 5 hours. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as eluent. After the completion of the reaction, the reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford the compound (5).

Yield: (75%). Pale yellow powder, M.P: 115–117^{0}C; IR (KBr) (νmax, cm^{-1}): 3413; 1659; 1190; 1367; 1390; 1140; 1H-NMR (500 MHz, $CDCl_3$) δ=8.51-7.56(m, 4H) 7.92 - 7.63 (t, 2H), 7.24-7.14 (d, J = 11.9 Hz, 2H), 7.04- 6.86(d, J = 15.5, 7.9 Hz, 2H), 5.27 - 4.81 (s, 2H), 2.50(s, H_2); 13C-NMR (126 MHz, $CDCl_3$) δ 169.70 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 129.83 (d, J = 3.6 Hz), 126.16 (s), 124.53 (d, J = 29.0 Hz), 127.56 (s), 66.54 (s), HRMS (ESI): 362.310; Elemental Analysis calculated for $C_{20}H_{15}N_3O_4$, C, 66.48; H, 4.18; N, 11.63 found C, 66.58; H, 4.28; N, 11.67%.

General Procedure for Synthesis of Compounds(6a-l):

A mixture of substituted benzoic acid (0.01mol) and 2-(4-(1,3-dioxo-1*H*-benzo[de]isoquinolin-2(3*H*)-yl)phenolxy)acetohydrazide (**5**) (0.01mol) in phosphoryl chloride (15ml) was refluxed for 6h. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (6:4) as eluent. After the completion of the reaction as indicated by TLC the reaction mixture was cooled and poured on to crushed ice (~200g) with continuous stirring. The solid mass separated was neutralized with sodium bicarbonate solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried in vacuum and recrystallized from absolute ethanol (95%) to afford the compounds **6a-l** in good yield.

Spectral Data for Representative Compounds (6a-l):

2-(4-((5-phenyl-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione(6a): Yield: (71%). white powder; M.P: 112-114^{0}C; IR (KBr) (νmax, cm^{-1}): 3321; 1647; 1587; 1070; 825; ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 8.58-7.96 (m, 4H), 8.21-8.01(d, J = 8.9 Hz, 1H), 7.56-7.01(d, J = 7.8 Hz, 1H), 7.92 - 7.53 (t, 2H), 7.24-7.04 (d, J = 11.9 Hz, 2H), 7.04- 6.86 (d, J = 15.5, 7.9 Hz, 2H), 5.27 - 4.81 (s, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (d, J = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (d, J = 29.0 Hz), 127.56 (s), 71.54 (s); HRMS (ESI): 449.120; Elemental Analysis calculated for $C_{27}H_{17}N_3O_4$, C, 72.48; H, 3.83; N, 9.39; found C, 72.58; H, 3.86; N, 9.49%.

2-(4-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6b): Yield: (65%). Gray colored powder; M.P: 116-118^{0}C; IR (KBr) (νmax, cm^{-1}): 3521; 1683; 1589; 1089; 844; ^{1}H-NMR (500 MHz, $CDCl_3$) δ= 8.58-7.96 (m, 4H), 8.21-8.01(d, J = 10.4 Hz, 1H), 7.56-7.01(d, J = 8.5 Hz, 1H), 7.92 - 7.53 (t, 2H), 7.24-7.04 (d, J = 11.9 Hz, 2H), 7.04- 6.86 (d, J = 15.5, 7.9 Hz, 2H), 5.27-4.81 (s, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (d, J = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (d, J = 29.0 Hz), 127.56 (s), 71.54 (s); HRMS (ESI): 482.108; Elemental Analysis calculated for $C_{27}H_{16}ClN_3O_4$, C, 67.30; H, 3.35; N, 8.72; found C, 67.34; H, 3.38; N, 8.79%.

2-(4-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6c): Yield: (60%). Colorless powder; M.P: 115-117^{0}C; IR (KBr) (νmax, cm^{-1}): 3522; 1658; 1585; 1066; 842; ^{1}H-NMR (500 MHz, $CDCl_3$) δ= 8.58-7.96 (m, 4H), 8.21-8.01(d, J = 11.3 Hz, 1H), 7.56-7.01(d, J = 10.3 Hz, 1H), 7.92 - 7.53 (t, 2H), 7.24-7.04 (d, J = 11.9 Hz, 2H), 7.04- 6.86(d, J = 15.5, 7.9 Hz, 2H), 5.27 - 4.81 (s, 2H); 13C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (d, J = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (d, J = 29.0 Hz), 127.56 (s), 71.54 (s); HRMS (ESI): 527.341; Elemental Analysis calculated for $C_{27}H_{16}BrN_3O_4$, C, 61.61; H, 3.06; N, 7.98; found C, 61.65; H, 3.46; N, 7.98%.

2-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6d): Yield: (72%). Colorless powder; M.P: 127-129^{0}C; IR (KBr) (νmax, cm^{-1}): 3219; 1680; 1514; 1109; ^{1}H-NMR (500 MHz, DMSO): δ = 8.51- 7.85 (m, *J* = 12Hz, 8H), 7.84 -7.49 (t, 2H), 7.43 - 7.11 (d, J = 9.2 Hz, 2H), 7.01- 6.82 (d, *J* = 5.4 Hz, 2H), 5.54- 2.67 (s, 2H); ^{13}C-NMR (126 MHz, DMSO): δ= 164.63 (s), 163.86 (s), 162.12 (s), 149.48 (s), 150.18 (s), 149.43(s), 137.61 (s), 137.16 (s), 135.96 (s), 132.25 (s), 132.07 (s),131.16 (s), 129.79 (s), 128.05 (s), 127.78 (s), 126.47 (s), 124.18 (s), 116.02 (s). 70.94 (s); HRMS (ESI): 492.442, Elemental Analysis calculated for $C_{27}H_{16}N_4O_6$,C, 65.85; H, 3.27; N, 11.38;; found C, 65.95; H, 3.47; N, 11.48; %.

2-(4-((5-(3-bromophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6e): Yield: (53%). Colorless powder; M.P: 120-122^{0}C; IR (KBr) (νmax, cm^{-1}): 3522; 1658; 1585; 1066; 825; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ= 8.58-7.28(m, 4H), 8.11-7.21(d, J = 10.4 Hz, 1H), 7.85-7.35(t, 2H), 7.72 - 7.56 (d, J = 8.7 Hz, 1H), 7.54-7.31 (m, *J* = 11Hz, 2H), 7.24-6.86 (dd, *J* = 15.5, 7.9 Hz, 2H), 5.27 - 4.81 (s, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (t, *J* = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (s), 123.41 (s), 71.54 (s); HRMS (ESI): 527.211; Elemental Analysis calculated for $C_{27}H_{16}BrN_3O_4$, C, 61.61; H, 3.06; N, 7.98; found C, 61.63; H, 3.45; N, 7.98%.

2-(4-((5-(3-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6f): Yield: (69%). Colorless powder; M.P: 134-136^{0}C; IR (KBr) (νmax, cm^{-1}): 3458; 1647; 1587; 1070; 825; ^{1}H-NMR (500 MHz, $CDCl_3$) δ= 8.58 -7.28 (m, 6H), 8.11-7.21(d, J = 10.3 Hz, 2H), 7.85-7.35(d, 2H), 7.72 - 7.56 (d, 1H), 7.51-7.31 (m, *J* = 11Hz, 2H), 7.24- 6.86(dd, *J* = 15.5, 7.9 Hz, 3H), 5.27 - 4.81 (s, 1H); 13C-NMR (126 MHz, CDCl3) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (t, *J* = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (s), 123.41 (s), 71.54 (s); HRMS (ESI): 464.34; Elemental Analysis calculated for $C_{27}H_{17}N_3O_5$, C, 69.97; H, 3.70; N, 9.07; found C, 69.97; H, 3.76; N, 9.37%.

2-(4-((5-(4-bromo-3-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6g): Yield: (54%). Gray powder; M.P: 137-139^{0}C; IR (KBr) (νmax, cm^{-1}): 3522; 3201; 1678; 1087; 823; 775; 752.; ^{1}H-NMR (500 MHz, DMSO): δ = 8.76 - 8.45 (s, 1H), 8.52 - 7.45 (m, 4H), 8.35 - 7.57 (d, J = 10.2 Hz, 2H), 8.18 - 7.01 (d, *J* = 11.0 Hz, 2H), 7.89 - 7.59 (t, *J* = 7Hz, 2H), 7.48 - 6.59 (d, *J* = 8.5 Hz, 1H), 7.11 - 6.5 (d, *J* = 7.5 Hz, 1H), 5.51 - 4.84 (s, 2H): ^{13}C-NMR (126 MHz, DMSO): δ = 166.22 (s), 164.35 (s),160.13 (s),158.48 (s), 154.23 (s, *J* = 5.3 Hz),138.19 (s), 137.61 (s),136.38 (s), 134.24 (s, *J* = 5.3 Hz), 131.15(s), 126.91 (s), 126.48 (s), 126.13 (s), 116.27 (s), 115.43 (s), 73.15 (s): HRMS (ESI): 572.134; Elemental Analysis calculated for $C_{27}H_{15}BrN_4O_6$,C, 56.76; H, 2.65; N, 9.81; found C, 56.79; H, 2.75; N, 9.86 %.

2-(4-((5-(4-chloro-3-aminophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6h): Yield: (61%). Yellow powder; M.P: 138-140^{0}C; IR (KBr) (νmax, cm^{-1}): 3480; 1678; 1334; 1087; 823; 760; 758.; ^{1}H-NMR (500 MHz, DMSO) δ = 8.62 - 7.48 (m, 4H), 7.18 - 7.89(t, *J* = 7Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.48 - 7.21 (d, J = 9.4 Hz, 2H), 7.35 - 7.10 (d, J = 9.9 Hz, 2H), 7.58- 7.01 (d, *J* = 11Hz, 2H), 7.53 - 6.45 (s, 1H), 6.49 - 5.69 (s, *J* = 2.7 Hz, 2H), 6.50 - 5.21(s, 2H): ^{13}C-NMR (126 MHz, DMSO): δ = 165.82 (s), 164.15(s), 159.73(s), 156.42 (s), 146.37(s),138.91(s), 138.68(s),131.88(s), 131.74 (s), 129.55 (s), 128.46(s), 126.38 (s), 126.60(s), 126.43(s), 126.13(s), 120.05(s), 120.10(s),116.93(s), 115.43(s), 72.47 (s): HRMS (ESI): 497.219; Elemental Analysis calculated for $C_{27}H_{17}ClN_4O_4$, C, 65.26; H, 3.45; N, 11.28 found C, 65.28; H, 3.65; N, 11.58;%.

2-(4-((5-(pyridin-2-yl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (i): Yield: (65%). Brown powder; M.P: 128-130^{0}C; IR (KBr) (νmax, cm^{-1}): 3435; 1690; 1070; ^{1}H-NMR (500 MHz, DMSO) δ = 8.65-7.51 (d, 1H), 8.58 -7.28(m, 4H), 8.14- 7.54 (d, J = 10.2 Hz, 1H), 6.56 – 7.88 (m, *J* = 13Hz, 3H), 6.51- 7.56 (t, *J* = 8Hz, 1H), 7.83-7.45(d, J = 7.4 Hz, 2H), 7.62 - 7.42 (d, J = 9.9 Hz, 2H), 5.32 - 4.61 (s, 2H); ^{13}C-NMR (126 MHz, DMSO): δ = 164.99, 163.22, 159.21, 157.15, 154.01, 149.83,135.59, 135.23, 130.29, 129.75,128.35, 128.03, 128.16, 127.73, 127.17, 126.79, 122.07, 114.70, 73.25,: HRMS (ESI): 448.121; Elemental Analysis calculated for $C_{26}H_{16}N_4O_4$,C, 69.64; H, 3.60; N, 12.49; found, C, 69.67; H, 3.72; N, 12.89;%.

2-(4-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (j): Yield: (58%). white powder; M.P: 114-115°C; IR (KBr) (νmax, cm^{-1}): 3321; 1647; 1587; 1070; 825; ^{1}H-NMR (500 MHz, $CDCl_3$) :- δ 8.58-7.96 (m, 4H), 8.21-8.01(d, J = 11.2 Hz, 1H), 8.10-7.10 (d, J = 7.9 Hz, 2H), 7.56-7.01(d, J = 8.4 Hz, 1H), 87.92 - 7.53 (t, 2H), 7.24-7.04 (d, J = 11.9 Hz, 2H), 7.04- 6.86(d, J = 15.5, 7.9 Hz, 2H), 5.27 - 5.11 (s, 2H), 3.58-2.53(s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (d, *J* = 3.6 Hz), 128.12(s),126.16 (s), 124.53 (d, *J* = 29.0 Hz), 127.56 (s), 116.10(d), 115.22(d), 71.54 (s), 56.52(s);HRMS (ESI): 478.121; Elemental Analysis calculated for $C_{28}H_{19}N_3O_5$,C, 70.43; H, 4.01; N, 8.80; found, C, 70.48; H, 4.05; N, 8.85%.

2-(4-((5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6k): Yield: (64%). Gray powder; M.P: 127-129^{0}C; IR (KBr) (νmax, cm^{-1}): 3219; 1680; 1514; 1109; 823; 775; ^{1}H-NMR (500 MHz, DMSO): δ= 8.76 - 8.45 (s, 1H), 8.52 - 7.45 (m, 4H), 8.35 - 7.57 (d, J = 11.4 Hz, 2H), 8.18 - 7.01 (d, *J* = 11Hz, 2H), 7.89 - 7.59(t, *J* = 7Hz, 2H), 7.48 - 6.59 (d, *J* = 8.5 Hz, 1H), 7.11 - 6.5 (d, *J* = 7.5 Hz, 1H), 5.51 - 4.84 (s, 2H): ^{13}C-NMR (126 MHz, DMSO): δ= 166.22 (s), 164.35 (s), 160.13 (s),158.48 (s), 154.23 (s, *J* = 5.3 Hz),148.33(s), 138.19 (s), 137.61 (s),136.38 (s), 134.24 (s, *J* = 5.3 Hz), 131.15(s), 126.91 (s), 126.48 (s), 126.13 (s), 116.27 (s), 115.43 (s), 73.15 (s): HRMS (ESI): 493.105; Elemental Analysis calculated for $C_{27}H_{16}N_4O_6$,C, 65.85; H, 3.27; N, 11.38 found C, 65.84; H, 3.28; N, 11.68%.

2-(4-((5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (6l): Yield: (70%). Pale yellow powder; M.P: 129-131^{0}C; IR (KBr) (νmax, cm^{-1}): 3321; 1647; 1587; 1070; 825; ^{1}H-NMR (500 MHz, $CDCl_3$) :- δ 8.58-7.96 (m, 4H), 8.21-8.01(d, J = 10.3 Hz, 1H), 8.10-7.10(d, J = 9.7 Hz, 2H), 7.56-7.01(d, J = 8.9 Hz, 1H), 87.92 - 7.53 (t, 2H), 7.24-7.04 (d, J = 11.9 Hz, 2H), 7.04- 6.86 (d, J = 15.5, 7.9 Hz, 2H), 5.27 - 5.11 (s, 2H), 3.89-2.53(s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 164.70(s), 163.92 (s), 157. 93 (s), 153.10 (s), 139.08 (s), 137.81 (s), 132.39 (s), 131.42(s), 129.83 (d,), 128.12(s),126.16 (s), 124.53 (d, *J* = 29.0 Hz), 127.56 (s), 112.39(d), 113.32(d), 71.54 (s), 56.52(s); HRMS (ESI): 507.321; Elemental Analysis calculated for $C_{29}H_{21}N_3O_6$,C, 68.63; H, 4.17; N, 8.28 found, C, 68.73; H, 4.27; N, 8.38 %.

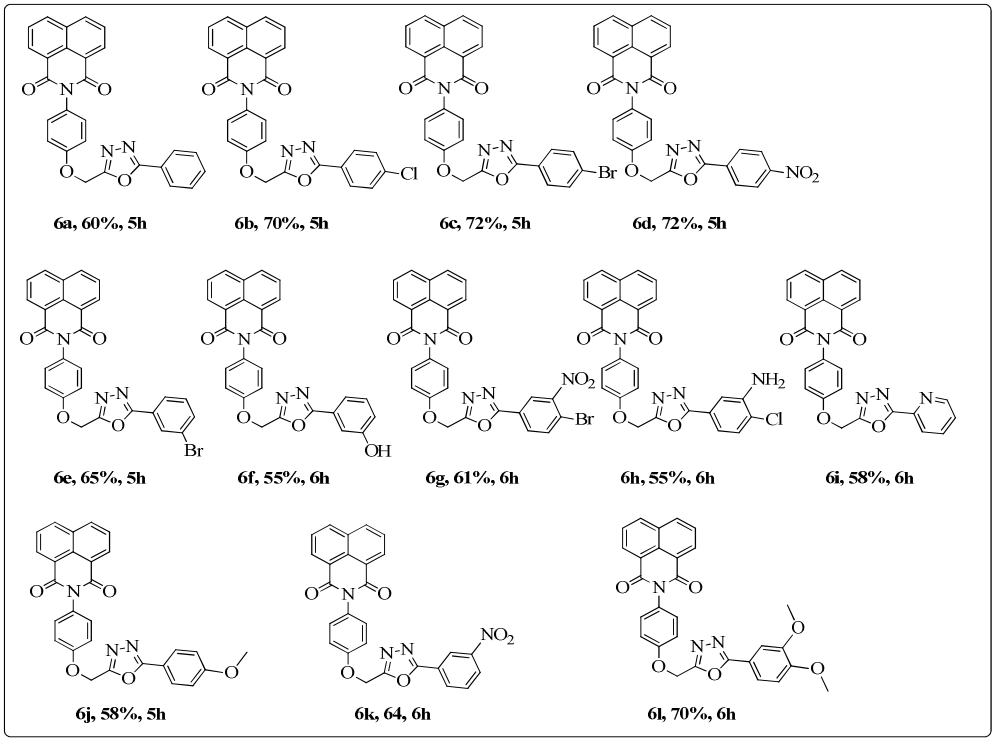


Table 1: Derivatives of 2-(4-((5-phenyl-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-*1H*-benzo[de]isoquinoline-1,3(2H)-dione **(6a-l)**

Pharmacological Studies

Test microorganisms

The four bacterial strains used in present study were collected from Osmania University. The bacteria used are *Escheria coli, Bacillus subtilis, Pseudomonas euroginosa and Staphylococcus aurous.*

Preparation of bacterial suspension

The screening of antibacterial and fungal activity was carried out by Agar well diffusion method. The test organisms were sub cultured on LB broth. Take 1 gram of LB broth and dissolve in 10ml of distilled water in a test tube and autoclaved at 15 pound pressures for 15 minutes and cool. Then add 10µl of bacterial culture to the broth in laminar air flow and stored at 4^{o}C in refrigerator to maintain the stock.

Results and Discussion

Chemistry

The aim of present work was to synthesize new series of 2-(4-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione derivatives (**6a-l**) from 2-(4-hydroxy phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (**3),** which was synthesized by 1,8-napthalic anhydride (0. 1mmol) react with 4-hydroxy aniline (0. 1mmol) in methanol as solvent for 4 hours under reflux condition. The compound (**3**) reacted with ethyl bromoacetate under base catalyzed condition to afford the corresponding ester derivatives (**4**). The compound (**4**) on treatment with hydrazine hydrate in the presence of ethanol gives corresponding hydrazinyl derivatives (**5**). The hydrazinyl derivatives were reacted with various substituted aromatic carboxylic acids in the

Presence of $POCl_3$ produceses the corresponding 2-(4-((5-phenyl-1,3,4-oxadiazol-2-yl)methoxy) phenyl)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione derivatives **(6a-l)** in good to excellent yield. All the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic techniques.

Antibacterial activity

The newly prepared compounds were screened for their anti-bacterial activity against *E. coli, S. aureus*, *P. aeruginosa*, and *Bacillus subtilis* at 100 and 200 µg/ mL concentration by using Ciprofloxacin as standard drug. The results of the above antimicrobial studies are given in **Table 2** (zone of inhibition). The results of the antimicrobial activity (zone of inhibition (mm)) of newly synthesized 1, 3, 4-oxadiazoles derivatives (**6a-l**) reveal that most of the compounds are more active than or as active as standard Ciprofloxacin drug. For example the compound **6f** and **6i** is more active against all 4 bacterial strains at 20, 30 and 40 µg/ml with compare to standard drug. Similarly all other compounds are more active/as active as standard drug. At the 100 and 200 µg/ml antimicrobial activity results (**table-2**) reveal that compound **6f** and **6i** are as potent against *S. aureus* with compare to standard drug. In the case of *B. subtilis* the compound **6f** and **6i** are more active. In the case of *E. coli* the compounds **6f** and **6i** are more active, whereas, the remaining compounds are moderately active with compare to standard drug. The compounds **6f** and **6i** are more active against *P. aeruginosa*.

Table-2. Antibacterial zone of inhibition (mm) of 1, 3, 4-oxadiazoles **(6a-i)**

Compounds	Conc.(µg/ml)	Zone of inhibition (mm)			
		S.aureus	*B.subtilis*	*E.coli*	*P.aeruginosa*
6a	100 200	15 17	11 19	23 24	19 21
6b	100 200	18 19	15 18	14 21	20 26
6c	100 200	12 14	16.5 18	12 16	21 23
6d	100 200	18 20	17 18	18 21	22 29
6e	100 200	20 18	19 18	21 20	24 26
6f	**100** **200**	**21** **23**	**20** **22**	**24** **25**	**30** **31**
6g	100 200	19 20.5	17 18.7	18 21	22 28
6h	100 200	18.6 19	15 18	14 22	23 25
6i	**100** **200**	**22** **24**	**19** **21.5**	**25** **26**	**31** **32**
C 6j	100 200	20 21	18 19.1	21.5 20.9	30 28
6k	100 200	19.5 20.5	20 19.7	22 21.1	25.8 22
6l	100	18	17.9	20	28.9

	200	19	18.2	22	30
Ciprofloxacin	100 200	23 24	21 22	26 27	32 33

Antifungal activity

The anti-fungal activity of the newly prepared compounds (**6a-l**) against *A. niger and C. albicans* are tested at 100 and 200 µg/ml concentration and the results are summaries in the **Table-3**. The result of the antifungal activity revealed that the compounds **6f** and **6i** are showing the same zone of inhibition as standard drug Voriconazole against *A. niger*. In the case of *C. albicans* the compounds **6f** and **6i** are showing the more zone of inhibition with compare to standard drug. Potent as standard drug against *A. niger*. In the case of *C. albicans* the compounds **6f** and **6i** is as active as standard drug.

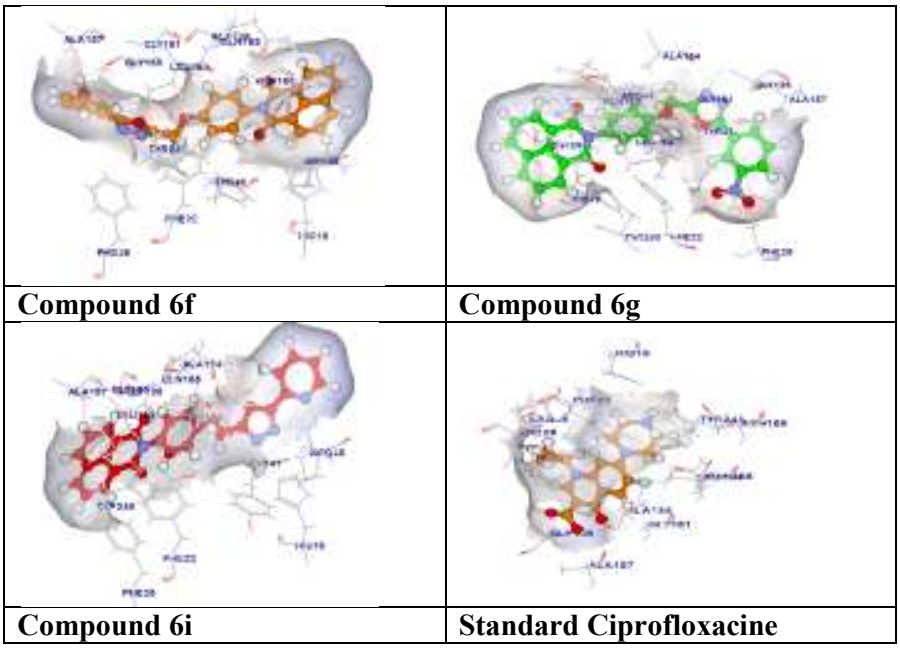
Docking studies

Exploration of molecular interaction of the newly synthesized 2-(4-((5-phenyl-1, 3, 4-oxadiazol-2-yl)methoxy)substituted phenyl)-1*H*-benzo [de]isoquinoline1, 3 (2*H*) dione derivatives (**6a-l**) as antibacterial and fungal agents. The molecular docking studies were performed by using Discovery Studio 2.1. The carotenoid dehydrosqualene synthase from Staphylococus aureus (PDB ID: 2ZCS) crystal were retrieved from Protein Data Bank (10.2210/pdb2zcs/pdb). Retrieved crystal structure of carotenoid dehydrosqualene synthase was cleaned and hydrogen atoms were added. All the hetero atoms were removed before docking study. The compounds used in the molecular docking studies were RB, RB1, RB2 and Ciprofloxacin on carotenoid dehydrosqualene synthase. The docking study of title compounds revealed the high docking scores (LibDock) and binding affinities, in the range of 140.228-124.448, as compared to Ciprofloxacin 136.559 **(Figure-2).** Thus the molecular docking studies results also support to the antimicrobial and antifungal activities.

Table-3. Antifungal zone of inhibition (mm) of 1, 3, 4-oxadiazoles, **(6a-i)**

Compounds	Conc.(µg/ml)	Zone of inhibition(mm)	
		A. niger	*C. albicans*
6a	100 200	18 21	19.5 22.3
6b	100 200	24 22.4	20 18.2
6c	100 200	17 19	20 21
6d	100 200	20 23	19.5 21
6e	100 200	21 24	20.6 19.2
6f	**100** **200**	**27** **29**	**23** **26**
6g	100 200	15 16.8	14.2 21
6h	100 200	24 22.8	20.3 17
6i	**100** **200**	**26.5** **28.9**	**23.8** **24.5**

6j	100 200	23 22	22.5 24.1
6k	100 200	23.9 24.1	21.1 22
6l	100 200	20 23.3	19.3 23
Voriconazole	100 200	28 30	24 26



Compound 6f | **Compound 6g**

Compound 6i | **Standard Ciprofloxacine**

Figure 2:- The molecular docking studies results

Conclusion

In conclusion, we have developed a new series of novel 2-(4-((5-phenyl-1, 3, 4-oxadiazol-2-yl)metho-xy)phenyl)-1**H**-benzo[de]isoquinoline-1,3(2**H**)-dione derivatives (**6a-l**) were synthesized and evaluated for their antibacterial and antifungal activity. The antibacterial results shows that compounds **6i** more than **6f** are as potent against *S. aureus* with compare to standard drug. In the case of *B. subtilis* the compounds **6f** more than **6i** are more active. In the case of *E.coli* the compounds **6i** more than **6f** are more active. The compounds **6f** and **6i** are more active against *P. aeruginosa*. The anti-fungal activity result shows that the compounds **6f** and **6i** are as active as standard drug Voriconazole against *A.niger*. In the case of *C. albicans* the compounds **6f** and **6i** are showing the same activity with compare to standard drug.

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