Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.5035

DESIGN, SYNTHESIS, AND BIO-EVALUATION OF NEW ISOINDOLINE-1,3-DIONE DERIVATIVES AS POSSIBLE ANTIMICROBIAL AND ANTIFUNGAL AGENT

Avinash Mishra[1*], Umesh Kumar[1], Satish Kumar Sharma

[1*]Department of Pharmaceutical Chemistry, Glocal university mirzapur Pole, Saharanpur, Uttar Pradesh India. ashok.sehgal87@gmail.com
[2]Department of Pharmacology Glocal University Mirzapur Pole, Saharanpur Uttar Pradesh India. pvc@theglocaluniverity.in

***Corresponding Author:** Avinash Mishra
Email: ashok.sehgal87@gmail.com

Abstract— New series of 4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dio xoisoindolin-2-yl) acetamides, and N-(4-(substituted phenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamides were synthesized. Synthesis of these compound design in two scheme (A & B)The initial step of the reaction in scheme A, involve the reaction phthalic anhydride with and glycine yielded 2-(1, 3-dioxoisoindolin-2-yl) acetic acid, further chlorination of this product form yielded 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride. The second step involves the reaction para-bromoaniline and yield N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide, the basic moiety was obtain by the reaction of hydroxyl chalcone i.e 4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dio xoisoindolin-2-yl) acetamides. Scheme B was design to substitute to bromide group on the 4^{th} position in the respective compound with the phenol group and further change the R with H,4-CH_3, 4-Cl, 2-Br, 3,4-Cl, 2-NO_2, 4-Br, 4-NO_2, 4-OCH_3 and 2-Cl. The confirmation of the newly synthsized compound by interpreting the essential analysis, spectral data, and alternative synthetic routes, Twenty of the synthesized compounds were screened for their antibacterial activity against S. *aureus*, and E. *coli* whereas AK1, BK1 and BK2 were the potential compound in this study. They were showing the highest antibacterial activity against the two selected microorganisms. The antifungal activity of these compounds was also tested against C. *albicans* and A. ***niger*** . Compounds AK4, and BK5 exhibited the best antifungal activity against C. *albicans* and A. ***niger*** in all the synthesized compound in series A & B respectively. The 4-(phenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dio xoisoindolin-2-yl) acetamides synthesized compound could show the bacteriostatic property through binding to cell membrane, previous studies shows that phthalimide moiety have potential to interaction with cytochrome P450 enzyme' of the fungus due to the their aromatic character further impair ergosterol synthesis of the fungal cell membrane results abnormalities in the fungus cell. The comparative study few of the selected, newly synthesized compounds validated moderate to good antimicrobial and antifungal effect were also compared with the standard drug ampicillin and clotrimazole respectively.

Keywords— Hydroxyl chalcone, Ampicillin, Clotrimazole, Phthalimide , Antimicrobial, Antifungal

I. INTRODUCTION

Repeated use of the antibiotics in narrow to broad infection is the main cause of the Antimicrobial resistance, it is a life-threatening problem in all over the world in the last two decades. Pathogens are accountable for common infections have developed resistance to antimicrobials agent, it directly impact to global health and placing a massive burden on the sector of health services **[11]. T**he exploration of new bioactive or synthetic agents has become enormously significant for stimulating health and in the advancement of more efficient antimicrobials [9]**.** Isoindoline-1, 3-dione (phthalimide) derivatives have been demonstrated to exhinbit various biological activities, such as anticancer [9] anti-inflammatory **[,** monoamine oxidase-B inhibitory potency [13], α-glucosidase inhibitory,anti-amyloid-β aggregation, antiepileptic [5], and AChE inhibitory activity **[10].** Nitogen (N) atom in the heterocyclic ring of Phthalic anhydride along with two unsymmetrically unsaturated C-X functional groups on the five-membered indole core exhibit the point of attraction to the various researcher [3]. However, this exceptional arrangement of the atom enhanced the difficulty of its synthetic pathways. In addition, glycine further para-bromoaniline is a privileged support for the design and development of new chemicals structure. Moreover, molecular modelling showed the intermediary moiety 2-(1, 3-dioxoisoindolin-2-yl) acetic acid, 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride , N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide, and 4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dio xoisoindolin-2-yl) acetamides has been obtain after with the chemical reaction of hydroxyl chalchone[2]. This research has been design by introducing two scheme (A & B) for the synthesis of new compounds is shown in Fig. 4 and 5. The synthesized compound 4-(phenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dio xoisoindolin-2-yl) acetamides could obstruct the growth of bacteria through binding to cell membrane, of the bacteria and the phthalimide scaffold might have potential interaction with the fungus due to the aromatic character of that moiety interacted with enzyme [8]. They inhibit the cytochrome P450 enzyme'and thus impair ergosterol synthesis cascade of membrane abnormalities in the fungus [17]. However, newly synthesized moiety active against certain bacteria as well as fungus, but the mechanism is not illustrated till now (compound B, Fig. 2) [34]. Starting with these findings, we were working the hybridization approach to alter the structure of the basic moiety that improve and reduce the resistance for multiple chemical /drug expanding their biological activity [36].

II MATERIALS AND METHODS

All chemicals and solvents were purchased from Sigma, CDH and Himedia. All chemicals used were of analytical grades and purified before used. The Glass wares were cleaned and dried before the use.

Chemistry

General Method Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide discs on **Perkin Elmer RX1**. The ^{1}H NMR spectra were recorded on a Bruker DRX-300 spectrophometer at 300 MHz in $CDCl_3$ and DMSO containing TMS as internal standard. All chemical shift values are reported in ppm (δ) **(rauf et al)** The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized in an iodine chamber [34]r. All the test compounds were recrystallized, dried and kept under vacuum desiccator. The computational properties (Physicochemical properties) of test compounds were computed by free online software (Chem Draw 12) and test compounds further subjected to biological evaluation against microbial strains for their antimicrobial activity [13].

Synthesis and Characterization of Compounds

Series A: Synthesis of isoindoline derivatives (AK1-10)

Step I. Synthesis of 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3)

Procedure A mixture of 2.96 gm (0.02 mole) of phthalic anhydride (1) and 1.50 gm (0.02 mole) of glycine (2) was taken in a 200 ml of beaker and heated for 30 minutes with continuous stirring at

150-155 ^{0}C by using oil bath. After cooling, the solid material was dissolved in hot methanol and the filtrate solution was diluted with 50 ml water and allowed to give crystalline product [23].

Step II. Synthesis of 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride (4)

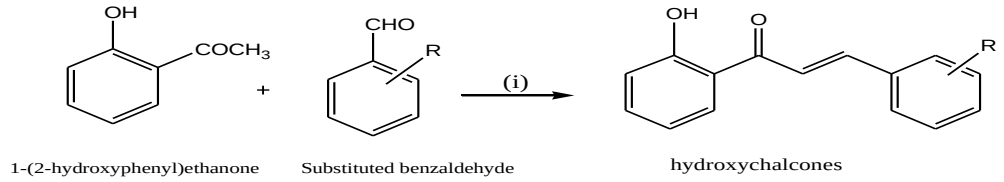
Procedure 2.05 gm (0.01 mole) of 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3) was dissolved in 100 ml of chloroform in a RBF and 1.45 ml (0.2 mole) of thionyl chloride was added. The reaction mixture was refluxed for 6 hr. The solvent and excess of thionyl chloride was removed under reduced pressure. The resulting solid residue (4) was recrystallized from acetone.

Step III. Synthesis of N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide (5) .

Procedure 2.23 gm (0.01 mole) of 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride (4) and 1.72 gm (0.02 mole) of para-bromoaniline (5) was dissolved in 100 ml of anhydrous acetonitrile in a 250 ml RBF. 2.76 gm (0.02 mole) anhydrous potassium carbonate was added. The reaction mixture was refluxed with stirring for 12 hr. The reaction mixture was filtered and solvent removed under pressure. The resulting solid residue was recrystallized from acetone afforded the compound (5).

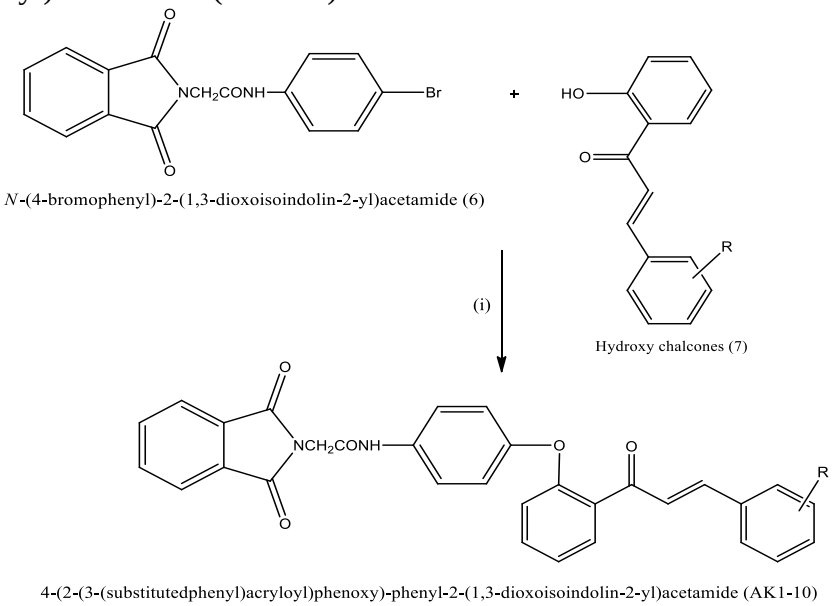
General procedure for the synthesis of hydroxychalcone (HC1-10)

Equimolar amount of ortho-hydroxyacetophenone and substituted benzaldehyde was dissolved in ethanol (50 ml) and aqueous potassium hydroxide (40%, 15ml) was added to it and stirred for 12 h at room temperature. The reaction mixture was kept overnight and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The solid separated was filtered and dried to obtain the various hydroxychalcones[9].



Scheme 1. Reagents and conditions: (i) Potassium hydroxide, stir at room temp for 12 hr

Step IV. Synthesis of 4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dio xoisoindolin-2-yl) acetamides (AK1-10)



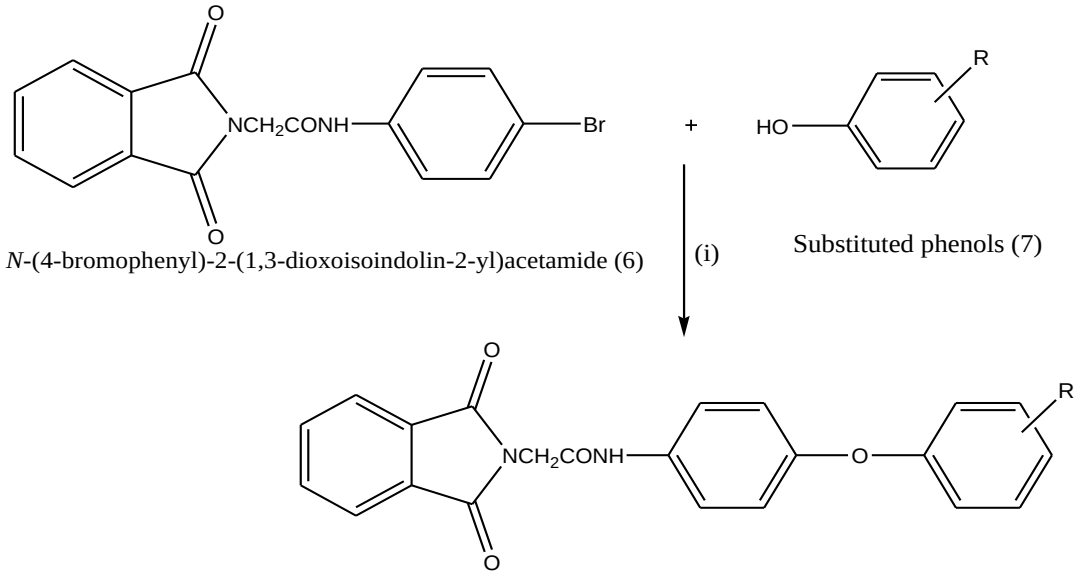
Scheme 1. Reagents and conditions: (i) Anhydrous acetonitrile, anhydrous potassium carbonate, reflux.

General procedure of the synthesis of 4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamides (AK1-10)

1.077 g (0.003 mole) of N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide (6) and 0.003 mole of substituted hydroxychalcone (7) was solubilize in 100 ml anhydrous acetonitrile in a 250 ml RBF. 0.82 gm (0.006 moles) then anhydrous potassium carbonate was added in the mixture [24]. The reaction mixture was refluxed with stirring for 12 hrs. The reaction mixture was filtered and solvent removed under pressure. The final product was recrystallized from ethanol the compound (AK1-10) [27].

Series B: Synthesis of isoindoline derivatives (BK1-10)

General procedure of the synthesis of N-(4-(substituted phenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamides (BK1-10)



N-(4-bromophenyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (6)

Substituted phenols (7)

N-(4-(substituted phenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamides (BK1-10)

Scheme 2. Reagents and conditions: (i) Anhydrous acetonitrile, anhydrous potassium carbonate, reflux.

General procedure of the synthesis of N-(4-(substituted phenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamides (BK1-10)

1.077 g (0.003 mole) of N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide (6) was dissolved in anhydrous acetonitrile in a 250 ml RBF. 0.003 mol of substituted phenol (7) and 0.82 gm (0.006 mole) anhydrous potassium carbonate was added. The reaction mixture was refluxed for 12 hrs. The reaction mixture was filtered and solvent removed under pressure. The obtained residue was recrystallized from ethanol afforded the compound (BK1-10).

III Computational Studies

A set of physicochemical properties was computed for the target compounds as well as standard drugs Ampicillin and Clotrimazole by using Chem 3D Ultra version 12.0 free software programs. The observations are depicted in Tables 7 & 8. The log P values, and other physicochemical descriptors include topological polar surface area, Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2), Connolly solvent excluded volume (SEV, A^3), molecular weight (MW), molar refractivity (MR), and Ovality were computed for test the compounds along with standard drugs by online software. The physicochemical descriptors include MW, logP, MR, Connolly Accessible Area, Connolly Molecular Area, Connolly Solvent Excluded

Volume, Ovality and tPSA are the major factors responsible for affecting the antimicrobial activity[30].

The lipophilicity of a molecule is a well-recognized as a crucial physicochemical factor that conditions the biological activity of a drug candidate. It determines not only the transport of molecules through biological membranes but also their ability to undergo complexation with blood proteins and binding to receptors. Knowledge of lipophilicity helps us understanding pharmacokinetic properties; including absorption, distribution, metabolism, and excretion (ADME) processes, as well as toxicity[43]. The lipophilicity of test compounds was for series A (4.21-5.42) and Series B (2.91-4.16) and within the range as compare with standard drugs which clearly shown penetrability of lipophilic cell membrane of bacteria by the test compounds.

The topological polar surface area (TPSA) as a chemical descriptor for passive molecular transport through membranes. TPSA allows for prediction of transport properties of drugs and has been linked to drug bioavailability. The topological polar surface area (tPSA) is a measure of a molecule's hydrogen bonding capacity and its value should not exceed certain limit. Generally, it has been seen that passively absorbed molecules with a TPSA > 140 $Å^2$ are thought to have low oral bioavailability. Results showed TPSA of test compounds for series A (92.78-144.59) and Series B (75.71-127.52) and within the range as compare with standard drugs and showed good oral bioavailability [46]

Molecular size is an important descriptor as most physicochemical properties and many biological properties are strongly size-related. Molecular size can be assessed in different ways. The molecular weight is easily calculated from the molecular formula. Also a simple atom count can be seen as a crude measure of molecular size. Molecular size is generally important for the permeability of compounds. The great majority of drugs on the market have molecular weights between 200 and 600 Daltons. Results showed molecular weight of test compounds for series A (502.52-592.59) and Series B (372.37-451.27) and within the range as compare with standard drugs[35].

Another size descriptor is the molar refractivity, which is directly related to the molar volume (molecular weight divided by the liquid density) and a function of the refractive index of the liquid, thus containing information about polarizability of the molecules. Molar refractivity (*MR*) descriptor is related to specific interactions with a target molecule and the electronic effects in the biological–chemical interaction, mainly for allosteric effects of interactions between the ligand-receptor. Results showed the molar refractivity of test compounds were for series A (144.36 - 166.11) and Series B (102.22- 111.43) and within the range as compare with standard drugs.

Ovality is defined as the ratio between the surface of the molecule and the surface of a sphere with the same volume [37]. Results showed the Ovality of test compounds were for series A (1.5734-1.8080) and Series B (1.5999- 1.6272) and within the range as compare with standard drugs.

The other descriptors values like Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2) and Connolly solvent excluded volume (SEV, A^3) of test compounds were within the range as compare with standard drugs38].

.

Fig. 1 Bacterial growth

Fig. 2 Antimicrobial effect of Ampicillin

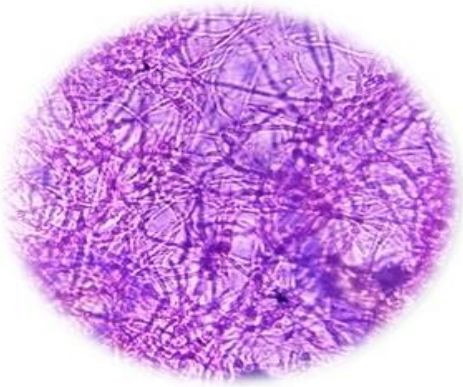


Fig. 3 Microscopy of the Fungal Growth

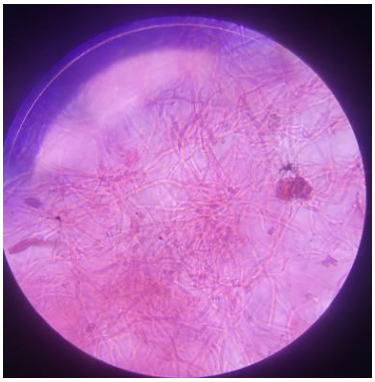


Fig. 4 Effect of the Clotrimazole of on Fungal Growth

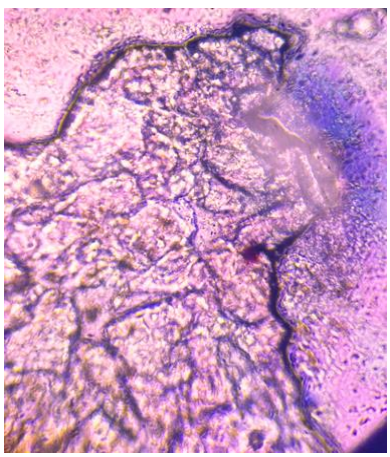


Fig. 5 Effect of AK1 on the growth of E.Coli

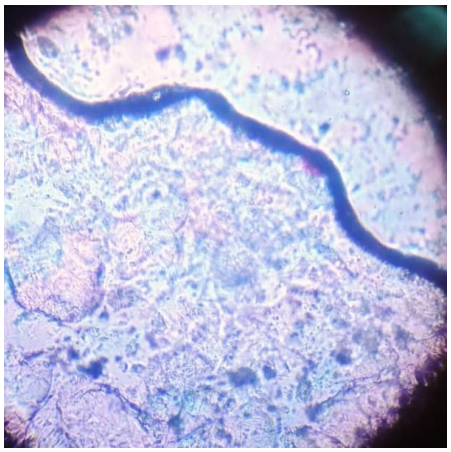


Fig. 6 Antifungal effect of AK4 compound

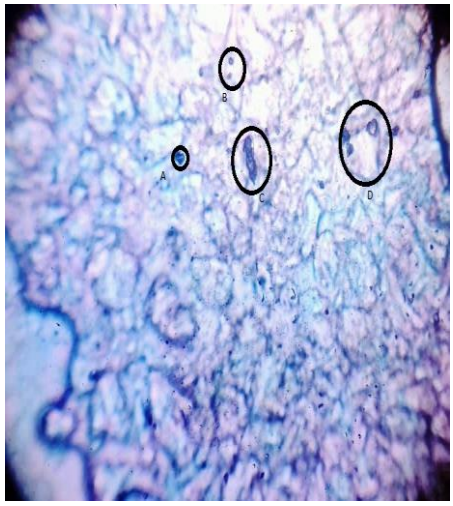


Fig. 7 Antifungal effect of BK5

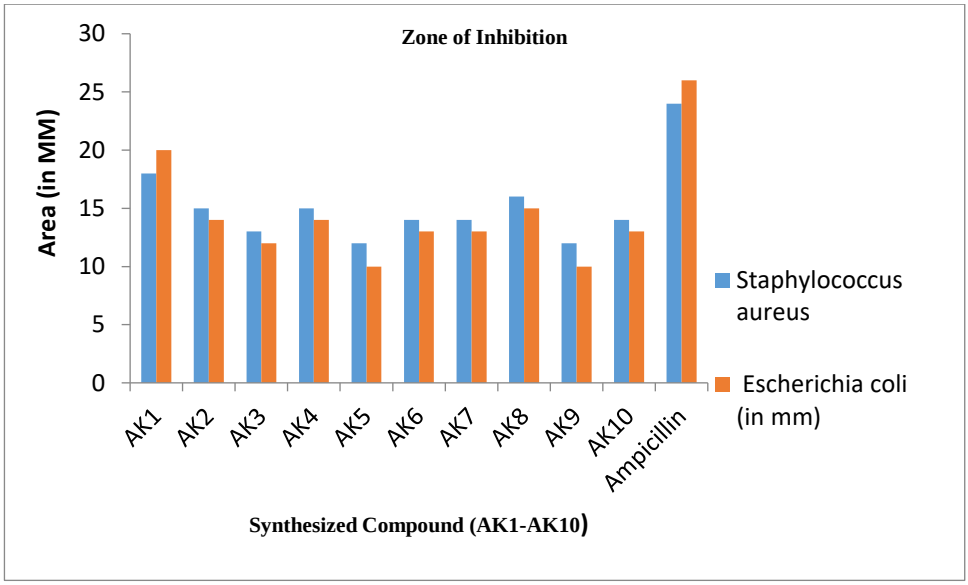


Fig. 8 Zone of inhibition of Synthesized Compound (AK1-AK10) against Staphyococcus and Escherichi coli

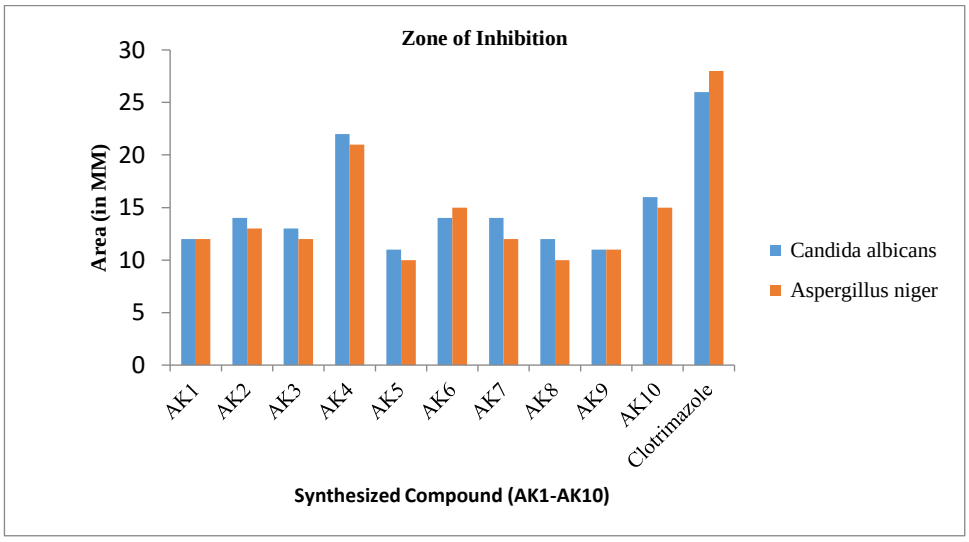


Fig. 9 Zone of inhibition of Synthesized Compound (AK1-AK10) against Candida albicans and Aspergillus niger

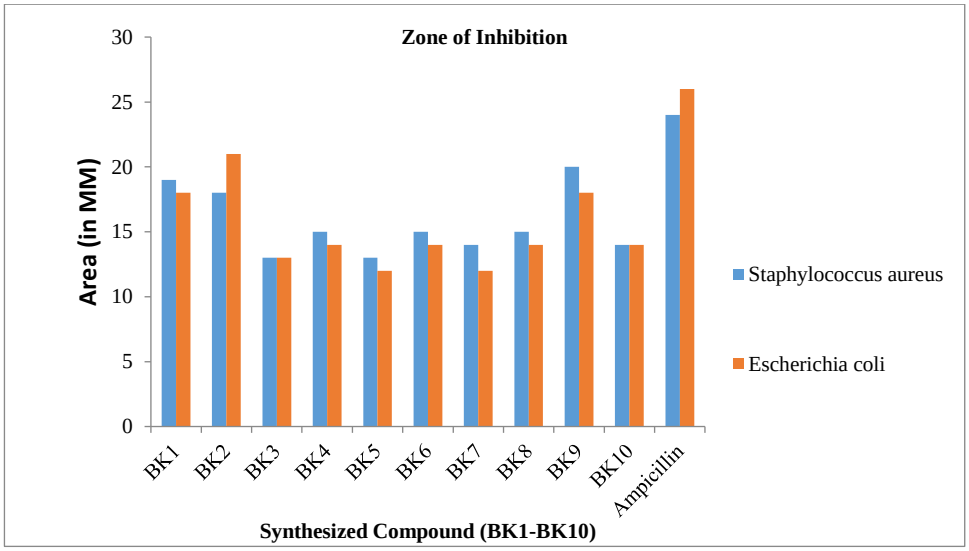


Fig. 10 Zone of inhibition of Synthesized Compound (BK1-BK10) against Staphyococcus and Escherichi coli

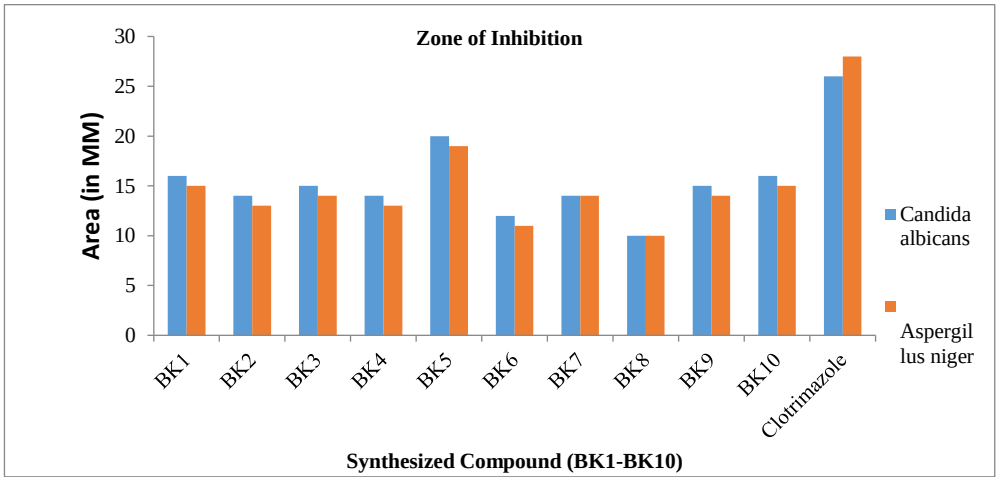


Fig. 11 Zone of inhibition of Synthesized Compound (BK1-BK10) against Candida albicans and Aspergillus niger

Table 1. The physical parameters of the hydroxychalcones (HC1-10)

S.No	Cpd. Code	R	M.P. (^{o}C)	R_{f} (n-Hexane: Ethyl acetate: 1:1)
1.	HC1	H	80-82	0.91
2.	HC2	3-NO_2	79-81	0.85
3.	HC3	4-CH_3	62-64	0.96
4.	HC4	4-F	63-65	0.84
5.	HC5	2, 3,4-OCH_3	61-63	0.90
6.	HC6	2-OCH_3	90-92	0.89
7.	HC7	4-$N(CH_3)_2$	52-54	0.88
8.	HC8	2-NO_2	60-62	0.68
9.	HC9	3,4,5 -OCH_3	105-107	0.74
10.	HC10	4-Br	64-66	0.70

Table 2: Physicochemical properties of Series A (AK1-10)

Cpd. Code.	MW[a]	MR[b]	tPSA[c]	CAA[d]	CMA[e]	CSEV[f]	Ov[g]	Log P
AK1	502.52	144.36	92.78	685.57	377.89	349.99	1.5734	4.59
AK2	547.51	NC	144.59	827.62	454.41	389.79	1.7609	4.74
AK3	516.54	150.26	92.78	825.54	451.40	386.65	1.7587	5.08
AK4	520.51	144.77	92.78	800.50	436.38	372.98	1.7415	4.75
AK5	592.59	166.11	120.47	901.65	505.07	441.12	1.8023	4.21
AK6	532.54	151.61	102.01	728.55	402.99	373.10	1.6078	4.46
AK7	545.58	159.54	96.02	868.12	477.98	412.40	1.7839	4.88
AK8	547.51	NC	144.59	710.74	395.36	367.70	1.5928	4.74
AK9	592.59	166.11	120.47	913.22	505.78	439.96	1.8080	4.21
AK10	581.41	152.05	92.78	827.48	452.92	389.85	1.7549	5.42
Clotrimazole	344.84	102.07	15.6	542.70	286.36	270.17	1.4168	5.19
Ampicillin	349.40	89.37	112.73	526.59	282.00	285.27	1.3456	-0.2

Table 3. Physicochemical properties of Series B (BK1-10)

Cpd. Code.	MW[a]	MR[b]	tPSA[c]	CAA[d]	CMA[e]	CSEV[f]	Ov[g]	Log P
BK1	372.37	102.22	75.71	626.41	326.92	274.16	1.6018	3.04
BK2	386.40	108.12	75.71	657.66	345.60	291.06	1.6271	3.53
BK3	406.82	106.83	75.71	649.84	341.44	292.55	1.6021	3.6
BK4	451.27	109.91	75.71	656.52	346.67	294.53	1.6193	3.87
BK5	441.26	111.43	75.71	670.09	354.73	306.6	1.6131	4.16
BK6	417.37	NC	127.52	662.96	350.49	297.26	1.6272	3.26
BK7	451.27	109.91	75.71	659.61	347.12	294.26	1.6224	3.87
BK8	417.37	NC	127.52	668.32	351.61	300.86	1.6193	3.26
BK9	402.40	109.47	84.94	671.81	353.16	301.56	1.6239	2.91
BK10	406.82	106.83	75.71	647.783	341.01	292.60	1.5999	3.6
Clotrimazole	344.84	102.07	15.6	542.70	286.36	270.17	1.4168	5.19
Ampicillin	349.40	89.37	112.73	526.59	282.00	285.27	1.3456	-0.2

MWa: Molecular Weight, **MRb:** Molar Refractivity, **tPSAc:** Topological Polar Surface Area, **CAAd:** Connolly Accessible Area, **CMAe:** Connolly Molecular Area, **CSEVf:** Connolly Solvent Excluded Volume, **Ovg:** Ovality

Table. 4 Spectral Data of Synthesized Compound (AK1 to AK10)

Cpd. Code	R(substitution)	Spectral Data
AK1	H	IR (KBr) υ (cm-1): 3370, 3090, 2970, 1730, 1620, 1590, 1430, 1310, 1251, 1120; 1H NMR (CDCl3, δ ppm): 9.88 (1H, NH), 8.20-6.64 (17H, Ar-H), 4.28 (2H, s, NCH2CO), 5.20-5.11 (2H, CH=CH).
AK2	3-NO_2	IR (KBr) υ (cm^{-1}): 3370, 3088, 2968, 1730, 1620, 1588, 1430, 1310, 1251, 1118; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.21-6.60 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.21-5.12 (2H, CH=CH).
AK3	4-CH_3	IR (KBr) υ (cm^{-1}): 3368, 3088, 2968, 1728, 1618, 1588, 1430, 1312, 1250, 1120; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.24-6.62 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.20-5.12 (2H, CH=CH), 3.80 (3H, CH_3).
AK4	4-F	IR (KBr) υ (cm^{-1}): 3370, 3090, 2968, 1728, 1620, 1590, 1430, 1312, 1250, 1120; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.22-6.63 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.21-5.10 (2H, CH=CH).
AK5	2, 3,4-OCH_3	IR (KBr) υ (cm^{-1}): 3360, 3088, 2970, 1730, 1618, 1588, 1430, 1310, 1250, 1118; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.18-6.60 (14H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.21-5.11 (2H, CH=CH), 3.99 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3).
AK6	2-OCH_3	3370, 3088, 2968, 1730, 1620, 1588, 1430, 1320, 1251, 1120; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.17-6.65 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.20-5.10 (2H, CH=CH), 3.90 (3H, s, OCH_3).
AK-7	4-$N(CH_3)_2$	IR (KBr) υ (cm^{-1}): 3360, 3090, 2970, 1728, 1618, 1590, 1430, 1320, 1251, 1118; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.10-6.45 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.20-5.14 (2H, CH=CH), 3.56 (3H, s, CH_3), 3.60 (3H, s, CH_3).
AK8	2-NO_2	IR (KBr) υ (cm^{-1}): 3370, 3090, 2968, 1730, 1620, 1590, 1430, 1310, 1250, 1120; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.20-6.62 (16H, Ar-H), 4.30 (2H, s, NCH_2CO), 5.21-5.12 (2H, CH=CH).
AK9	3,4,5 -OCH_3	IR (KBr) υ (cm^{-1}): 3370, 3088, 2970, 1728, 1620, 1588, 1426, 1312, 1250, 1118; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.10-6.59 (14H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.20-5.10 (2H, CH=CH), 3.98 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3).
AK10	4-Br	IR (KBr) υ (cm^{-1}): 3360, 3090, 2968, 1730, 1620, 1590, 1420, 1310, 1251, 1120; 1H NMR ($CDCl_3$, δ ppm): 9.88 (1H, NH), 8.31-6.60 (16H, Ar-H), 4.28 (2H, s, NCH_2CO), 5.21-5.16 (2H, CH=CH).

Table. 5 Spectral Data of Synthesized Compound (BK1 to BK10)

Cpd. Code	R(substitution)	Spectral Data
BK1	H	IR (KBr) υ (cm^{-1}): 3380, 3010, 2980, 1740, 1660, 1590, 1410, 1340, 1210, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.36-6.58 (13H, Ar-H), 4.30 (2H, s, CH_2CO).
BK2	4-CH_3	IR (KBr) υ (cm^{-1}): 3378, 3010, 2982, 1740, 1660, 1588, 1410, 1340, 1220, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.00 (1H, NH), 8.48-6.60 (12H, Ar-H), 4.30 (2H, s, CH_2CO 3.30 (3H, s, CH_3).
BK3	4-Cl	IR (KBr) υ (cm^{-1}): 3380, 3008, 2980, 1742, 1660, 1590, 1410, 1340, 1220, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.40-6.64 (12H, Ar-H), 4.30 (2H, s, CH_2CO).
BK4	2-Br	IR (KBr) υ (cm^{-1}): 3380, 3010, 2980, 1740, 1660, 1590, 1410, 1342, 1220, 1082; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.38-6.59 (12H, Ar-H), 4.30 (2H, s, CH_2CO).
BK5	3,4-Cl	IR (KBr) υ (cm^{-1}): 3382, 3010, 2978, 1740, 1658, 1590, 1410, 1342, 1220, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.20-6.70 (11H, Ar-H), 4.30 (2H, s, CH_2CO).
BK6	2-NO_2	IR (KBr) υ (cm^{-1}): 3380, 3010, 2980, 1740, 1660, 1590, 1410, 1340, 1221, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.00 (1H, NH), 8.10-6.62 (12H, Ar-H), 4.30 (2H, s, CH_2CO).
BK-7	4-Br	IR (KBr) υ (cm^{-1}): 3380, 3010, 2980, 1740, 1660, 1590, 1410, 1342, 1220, 1082; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.38-6.59 (12H, Ar-H), 4.30 (2H, s, CH_2CO).
BK8	4-NO_2	IR (KBr) υ (cm^{-1}): 3380, 3010, 2980, 1740, 1660, 1590, 1410, 1340, 1221, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.00 (1H, NH), 8.10-6.62 (12H, Ar-H), 4.30 (2H, s, CH_2CO).
BK9	4-OCH_3	IR (KBr) υ (cm^{-1}): 3388, 3010, 2980, 1740, 1658, 1590, 1410, 1340, 1220, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.13-6.58 (12H, Ar-H), 4.30 (2H, s, CH_2CO), 3.74 (3H, s, OCH_3).
BK10	2-Cl	IR (KBr) υ (cm^{-1}): 3380, 3008, 2980, 1742, 1660, 1590, 1410, 1340, 1220, 1080; 1H NMR ($CDCl_3$, δ ppm): 10.02 (1H, NH), 8.40-6.64 (12H, Ar-H), 4.30 (2H, s, CH_2CO).

Table 6. Percentage Yield, Melting Point Range, And Rf Value of synthesized compound Scheme A & B

S.no	Chemical Formula	Percentage yield	Melting range	Rf value	Mobile phase
1.	2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3)	84.00%	188-190 oC	0.94	n-Hexane: ethyl acetate: (1:1)
2.	2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride	78.00%	78-80 oC	0.8	n-Hexane: ethyl acetate: (1:2)
3.	N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide	62%	48-52 oC	0.68	n-Hexane: ethyl acetate: (2:1)
4.	4-(2-(3-(substituted phenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamides	58%	72-74 oC	0.69	n-Hexane: ethyl acetate: (1:1)
5.	4-(2-(3-(3-nitrophenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dioxoisoindolin-2-yl) acetamide	65%	105-107 oC	0.75	n-Hexane: ethyl acetate: (1:1)
6.	4-(2-(3-(4-methylphenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dioxoisoindolin-2-yl) acetamide	62	82-84 oC	0.7	n-Hexane: ethyl acetate: (1:1)
7.	4-(2-(3-(4-fluorophenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dioxoisoindolin-2-yl) acetamide	66	102-104 oC	0.73	n-Hexane: ethyl acetate: (1:1)
8.	4-(2-(3-(2, 3, 4-trimethoxyphenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamide	75	108-110 oC	0.78	n-Hexane: ethyl acetate: (1:1)
9.	4-(2-(3-(2-methoxyphenyl)acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamide	68	104-106 oC	0.68	n-Hexane: ethyl acetate: (1:1)

10.	4-(2-(3-(4-dimethylaminophenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamide	71	99-101 oC	0.67	n-Hexane: ethyl acetate: (1:1)
11.	4-(2-(3-(2-nitrophenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dioxoisoindolin-2-yl) acetamide	65	112-114 oC	0.87	n-Hexane: ethyl acetate: (1:1)
12.	4-(2-(3-(3, 4, 5-trimethoxyphenyl) acryloyl) phenoxy)-phenyl-2-(1, 3-dioxoisoindolin-2-yl) acetamide	76	92-94 oC	0.9	n-Hexane: ethyl acetate: (1:1)
13.	4-(2-(3-(4-bromophenyl) acryloyl) phenoxy)-phenyl-2-(1,3-dioxoisoindolin-2-yl) acetamide	78	115-117 oC	0.87	n-Hexane: ethyl acetate: (1:1)
14.	N-(4-(phenoxy) phenyl)-2-(1, 3-dioxoisoindo lin -2-yl) acetamide	68	100-102 oC	0.78	n-Hexane: ethyl acetate: (1:1)
15.	N-(4-(4-methylphenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	74	96-98 oC	0.76	n-Hexane: ethyl acetate: (1:1)
16.	N-(4-(4-chlorophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	65	112-114 oC	0.8	n-Hexane: ethyl acetate: (1:1)
17.	N-(4-(2-bromophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	68	120-122 oC	0.84	n-Hexane: ethyl acetate: (1:1)
18.	N-(4-(3, 4-dichlorophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	62	126-128 oC	0.82	n-Hexane: ethyl acetate: (1:1)
19.	N-(4-(2-nitrophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	54	106-108 oC	0.79	n-Hexane: ethyl acetate: (1:1)
20.	N-(4-(4-bromophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	70	115-117 oC	0.69	n-Hexane: ethyl acetate: (1:1)
21.	N-(4-(4-nitrophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	72	114-116 oC	0.74	n-Hexane: ethyl acetate: (1:1)
22.	N-(4-(4-methoxyphenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	75	92-94 oC	0.88	n-Hexane: ethyl acetate: (1:1)
23.	N-(4-(2-chlorophenoxy) phenyl)-2-(1, 3-dioxoisoindolin -2-yl) acetamide	75	97-99 oC	0.83	n-Hexane: ethyl acetate: (1:1)

IV Summary and Conclusion

Summary:

Series A

The target compounds **AK1-10** were prepared as outlined in Scheme **1**. An equimolar mixture of phthalic anhydride (1) and glycine (2) was taken in a beaker and heated for 30 minutes with continuous stirring at 150-155 ^{0}C by using oil bath. After cooling, the solid material was dissolved in hot methanol and the filtrate solution was diluted with 50 ml water and allowed to give crystalline product 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3). 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3) was dissolved in chloroform and thionyl chloride was added in a RBF. The reaction mixture was refluxed for 6 hr and excess of thionyl chloride was removed afforded 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride (4) which refluxed with para-bromoaniline (5) in presence of anhydrous potassium carbonate in anhydrous acetonitrile for 12 hr [19]. The resulting solid residue was recrystallized from acetone afforded the compound N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide (6) which further reacted with substituted hydroxychalcone (7) in presence of anhydrous potassium carbonate in anhydrous acetonitrile in a RBF for 12 hr. The reaction mixture was filtered and solvent removed under pressure. The obtained resulting product was recrystallized from ethanol afforded the compound (AK1-10). The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of melting point, TLC, IR and NMR spectroscopic method. The test compounds obtained in good percentage yield (58-78) and having NH stretching at 3370, and C=O stretching at 1730, 1620 in IR spectra, broad singlet NH peak at 9.88 and singlet peak of NCH_2CO at 4.28 in H1-NMR spectra confirmed the formation of test compounds.

The molecular property prediction was computed for the test compounds by free online software. All test compounds have molecular weight under 592.59 and have molar refractivity under 166.11.

Topological polar surface area (tPSA) values for the test compounds were well within these limits (92.78-144.59). The log P values of test compounds were (4.21-5.42) within the range and shown that these compounds have a potential to effectively cross the cell membrane of microbes and other molecular descriptors viz: Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2) , Connolly solvent excluded volume (SEV, A^3) and Ovality of test compounds were within the range as compare with standard drugs[9].
The test compounds (AK1-10) were tested for antimicrobial activity against bacterial strains *Staphylococcus aureus* (Gram Positive), *Escherichia Coli* (Gram Negative) *and fungal strains Candida albicans* and *Aspergillus niger* by agar diffusion method. Most of the test compounds in this series were inactive and zone of inhibition was below 18 mm except AK1 and AK4. The test compound **AK1** showed greater activity against *Staphylococcus aureus* (Gram Positive), *Escherichia Coli* (Gram Negative) bacteria but test compound **AK4** containing halogen atom at 4^{th} position (4-Fluoro) on aromatic ring (electron withdrawing group) showed the best antifungal activity in fig 5 [20].

Series B

The target compounds **BK1-10** were prepared as outlined in Scheme **2**. An equimolar mixture of phthalic anhydride (1) and glycine (2) was taken in a beaker and heated for 30 minutes with continuous stirring at 150-155 ^{0}C by using oil bath. After cooling, the solid material was dissolved in hot methanol and the filtrate solution was diluted with 50 ml water and allowed to give crystalline product 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3). 2-(1, 3-dioxoisoindolin-2-yl) acetic acid (3) was dissolved in chloroform and thionyl chloride was added in a RBF. The reaction mixture was refluxed for 6 hr and excess of thionyl chloride was removed afforded 2-(1, 3-dioxoisoindolin-2-yl) acetyl chloride (4) which refluxed with para-bromoaniline (5) in presence of anhydrous potassium carbonate in anhydrous acetonitrile for 12 hr. The resulting solid residue was recrystallized from acetone afforded the compound N-(4-bromophenyl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide (6) which further reacted with substituted phenols (7) in presence of anhydrous potassium carbonate in anhydrous acetonitrile in a RBF for 12 hr. The reaction mixture was filtered and solvent removed under pressure. The obtained resulting product was recrystallized from ethanol afforded the compound (BK1-10). The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of melting point, TLC, IR and NMR spectroscopic method. The test compounds obtained in good percentage yield (54-75) and having NH stretching at 3380, and C=O stretching at 1740, 1660 in IR spectra, broad singlet NH peak at 10.02 and singlet peak of CH_2CO at 4.30 in H1-NMR spectra confirmed the formation of test compounds.
The molecular property prediction was computed for the test compounds by free online software [36].
All test compounds have molecular weight under 451.27 and have molar refractivity under 111.43. Topological polar surface area (tPSA) values for the test compounds were well within these limits (75.71-127.52). The log P values of test compounds were (2.91-4.16) within the range and shown that these compounds have a potential to effectively cross the cell membrane of microbes and other molecular descriptors viz: Connolly solvent accessible surface area (SAS, A^2), Connolly molecular surface area (MSA, A^2) , Connolly solvent excluded volume (SEV, A^3) and Ovality of test compounds were within the range as compare with standard drugs [5].
The test compounds (BK1-10) were tested for antimicrobial activity against bacterial strains Staphylococcus aureus (Gram Positive), Escherichia Coli (Gram Negative) and fungal strains Candida albicans and Aspergillus niger by agar diffusion method. Among the compounds, BK1, BK2 BK5 and BK9 were showed potent antimicrobial activity6]. The test compound **BK1** showed best activity against Gram Negative bacteria (Escherichia Coli) and test compound **BK9** containing methoxy group at 4^{th} position (4-OCH_3) on aromatic ring showed the best activity against Gram

Positive bacteria (Staphylococcus aureus). The 3, 4-dichloro analog (BK5) showed potent antifungal activity in Fig 6, against Candida albicans and Aspergillus niger [31].

Conclusion:

Series of isoindoline derivatives (AK1-10& BK1-10) were synthesized, characterized and evaluated for antimicrobial activity. The test compound AK1 and AK4 (Series A) were post potent antimicrobials and BK1, BK2, BK5 and BK9 (Series B) were post potent antimicrobials. These analogs are also further required for the refinement of the antimicrobial study which could be better to treat the microbial infection. After the comparison of zone of inhibition of newly synthesized compound (AK1 to AK10) in scheme , compound Ak1 has maximum zone of inhibition against E.coli (20mm) and S.aureus (18mm) whereas Compund AK4 also has maximum zone of inhibition against C. albicans (22mm) and Aspergillus niger (21mm). The newly synthesized Compound by scheme 2 (BK1 to BK10) out of 10 only 4 compound (BK1,BK2,BK4 and BK9) BK1 Shows the has maximum zone of inhibition against E.coli (18mm) and S.aureus (19mm) whereas Compund BK2 has maximum zone of inhibition against E.coli (21mm) and Aspergillus niger (21mm) shown in table 6.

Bibliography

[1]. Ahmad, I., Pawara, R. H., Girase, R. T., Pathan, A. Y., Jagatap, V. R., Desai, N., et al. (2022, June). Synthesis, Molecular Modeling Study, and Quantum-Chemical-Based Investigations of Isoindoline-1,3-diones as Antimycobacterial Agents. *ACS Omega, 7*, 21820–21844.

[2]. Ahmed, H. E., Abdel-Salam, H. A., & Shaker, M. A. (2016, June). Synthesis, characterization, molecular modeling, and potential antimicrobial and anticancer activities of novel 2-aminoisoindoline-1,3-dione derivatives. *Bioorganic Chemistry, 66*, 1–11.

[3]. Aman, H., Huang, Y.-C., Liu, Y.-H., Tsai, Y.-L., Kim, M., Hsieh, J.-C., et al. (2021, November). Cobalt-Catalyzed Cyclization of 2-Bromobenzamides with Carbodiimides: A New Route for the Synthesis of 3-(Imino)isoindolin-1-ones. *Molecules, 26*, 7212.

[4]. Balouiri, M., Sadiki, M., & Ibnsouda, S. K. (2016, April). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis, 6*, 71–79.

[5]. Campos-Rodríguez, C., Trujillo-Ferrara, J. G., Alvarez-Guerra, A., Vargas, I. M., Cuevas-Hernández, R. I., Andrade-Jorge, E., et al. (2019, January). Neuropharmacological Screening of Chiral and Non-chiral Phthalimide- Containing Compounds in Mice: in vivo and in silico Experiments. *Medicinal Chemistry, 15*, 102–118.

[6]. Grauso, L., Teta, R., Esposito, G., Menna, M., & Mangoni, A. (2019). Computational prediction of chiroptical properties in structure elucidation of natural products. *Natural Product Reports, 36*, 1005–1030.

[7]. Hassanzadeh, F., Hassanzadeh, M., khodarahmi, G., Rostami, M., Azimi, F., Nadri, H., et al. (2021). Design, synthesis, and bio-evaluation of new isoindoline-1,3-dione derivatives as possible inhibitors of acetylcholinesterase. *Research in Pharmaceutical Sciences, 16*, 482.

[8]. Kolukisaoglu, Ü., Wendler, C., Goerdes, D., Diener, A., & Thurow, K. (2010, June). Inhibitory effects of phthalimide derivatives on the activity of the hepatic cytochrome P450 monooxygenases CYP2C9 and CYP2C19. *Journal of Enzyme Inhibition and Medicinal Chemistry, 25*, 876–886.

[9]. Ma, L., Yang, Z., Li, C., Zhu, Z., Shen, X., & Hu, L. (2011, January). Design, synthesis and SAR study of hydroxychalcone inhibitors of human β-secretase (BACE1). *Journal of Enzyme Inhibition and Medicinal Chemistry, 26*, 643–648.

[10]. Mohammadi-Farani, A., Abdi, N., Moradi, A., & Aliabadi, A. (2017). 2-(2-(4-Benzoylpiperazin-1-yl)ethyl)isoindoline-1,3-dione derivatives: Synthesis, docking and acetylcholinesterase inhibitory evaluation as anti-alzheimer agents. *Iranian Journal of Basic Medical Sciences, 20*.

[11]. Morrison, L., & Zembower, T. R. (2020, October). Antimicrobial Resistance. *Gastrointestinal Endoscopy Clinics of North America, 30*, 619–635.
[12]. Rauf, A., Shah, A., Abbas, S., Rana, U. A., Khan, S. U.-D., Ali, S., et al. (2015, March). Synthesis, spectroscopic characterization and pH dependent photometric and electrochemical fate of Schiff bases. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 138*, 58–66.
[13]. Sang, Z., Wang, K., Wang, H., Yu, L., Wang, H., Ma, Q., et al. (2017, November). Design, synthesis and biological evaluation of phthalimide-alkylamine derivatives as balanced multifunctional cholinesterase and monoamine oxidase-B inhibitors for the treatment of Alzheimer's disease. *Bioorganic & Medicinal Chemistry Letters, 27*, 5053–5059.
[14]. Shin, J., Kim, J.-E., Lee, Y.-W., & Son, H. (2018, March). Fungal Cytochrome P450s and the P450 Complement (CYPome) of Fusarium graminearum. *Toxins, 10*, 112.
[15]. Su, M., Cao, J., Huang, J., Liu, S., Im, D., Yoo, J.-W., et al. (2017, January). The In Vitro and In Vivo Anti-Inflammatory Effects of a Phthalimide PPAR-γ Agonist. *Marine Drugs, 15*, 7.
[16]. Wang, H., Yuan, H., Li, S., Li, Z., & Jiang, M. (2016, February). Synthesis, antimicrobial activity of Schiff base compounds of cinnamaldehyde and amino acids. *Bioorganic & Medicinal Chemistry Letters, 26*, 809–813.
[17]. Zhang, X., Guo, J., Cheng, F., & Li, S. (2021). Cytochrome P450 enzymes in fungal natural product biosynthesis. *Natural Product Reports, 38*, 1072–1099.
[18]. Abdel-Aziz, A. A.-M., El-Azab, A. S., Abu El-Enin, M. A., Almehizia, A. A., Supuran, C. T., & Nocentini, A. (2018, October). Synthesis of novel isoindoline-1,3-dione-based oximes and benzenesulfonamide hydrazones as selective inhibitors of the tumor-associated carbonic anhydrase IX. *Bioorganic chemistry, 80*, 706-713.
[19]. Afrakssou, Z., Rodi, Y. K., Capet, F., Essassi, E. M., & Ng, S. W. (2011, August). 1,3-Bis[3-(1,3-dioxoisoindolin-2-yl)prop-yl]-1H-anthra[1,2-d]imidazole-2,6,11(3H)-trione. *Acta crystallographica. Section E, Structure reports online, 67*(Pt 8), o2137.
[20]. Ahmad, I., Pawara, R. H., Girase, R. T., Pathan, A. Y., Jagatap, V. R., Desai, N., et al. (2022, June). Synthesis, Molecular Modeling Study, and Quantum-Chemical-Based Investigations of Isoindoline-1,3-diones as Antimycobacterial Agents. *ACS omega, 7*(25), 21820-21844.
[21]. Akkurt, M., Karaca, S., Jarrahpour, A. A., Zarei, M., & Büyükgüngör, O. (2008, April). 2-[1-(4-Ethoxy-phen-yl)-2-oxo-4-styryl-azetidin-3-yl]isoindoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 64*(Pt 5), o924.
[22]. Alanazi, M. M., Almehizia, A. A., Bakheit, A. H., Alsaif, N. A., Alkahtani, H. M., & Wani, T. A. (2019, March). Mechanistic interaction study of 5,6-Dichloro-2-[2-(pyridin-2-yl)ethyl]isoindoline-1,3-dione with bovine serum albumin by spectroscopic and molecular docking approaches. *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society, 27*(3), 341-347.
[23]. Al-Ghorbani, M., Alharbi, O., Al-Odayni, A.-B., & Abduh, N. A. (2023, August). Quinoline- and Isoindoline-Integrated Polycyclic Compounds as Antioxidant, and Antidiabetic Agents Targeting the Dual Inhibition of α-Glycosidase and α-Amylase Enzymes. *Pharmaceuticals (Basel, Switzerland), 16*(9).
[24]. Aliabadi, A., Foroumadi, A., Mohammadi-Farani, A., & Garmsiri Mahvar, M. (2013, October). Synthesis and Evaluation of Anti-acetylcholinesterase Activity of 2-(2-(4-(2-Oxo-2-phenylethyl)piperazin-1-yl) ethyl)Isoindoline-1,3-dione Derivatives with Potential Anti-Alzheimer Effects. *Iranian journal of basic medical sciences, 16*(10), 1049-54.
[25]. Almeida, M. L., Oliveira, M. C., Pitta, I. R., & Pitta, M. G. (2020). Advances in Synthesis and Medicinal Applications of Compounds Derived from Phthalimide. *Current organic synthesis, 17*(4), 252-270.
[26]. Andrade-Jorge, E., Bribiesca-Carlos, J., Martínez-Martínez, F. J., Soriano-Ursúa, M. A., Padilla-Martínez, I. I., & Trujillo-Ferrara, J. G. (2018, June). Crystal structure, DFT

calculations and evaluation of 2-(2-(3,4-dimethoxyphenyl)ethyl)isoindoline-1,3-dione as AChE inhibitor. *Chemistry Central journal, 12*(1), 74.

[27]. Asad, M., Oo, C.-W., Osman, H., Hemamalini, M., & Fun, H.-K. (2011, July). 2-[(E)-(2,4-Dichloro-benzyl-idene)amino]-isoindoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 67*(Pt 7), o1712.

[28]. Azimi, S., Zonouzi, A., Firuzi, O., Iraji, A., Saeedi, M., Mahdavi, M., et al. (2017, September). Discovery of imidazopyridines containing isoindoline-1,3-dione framework as a new class of BACE1 inhibitors: Design, synthesis and SAR analysis. *European journal of medicinal chemistry, 138*, 729-737.

[29]. Bai, L.-G., Chen, M.-T., Xiao, D.-R., Zhao, L.-B., & Luo, Q.-L. (2018, August). Access to Multisubstituted Furan-3-carbothioates via Cascade Annulation of α-Oxo Ketene Dithioacetals with Isoindoline-1,3-dione-Derived Propargyl Alcohols. *The Journal of organic chemistry, 83*(15), 7648-7658.

[30]. Bao, Y., Xing, M., Matthew, N., Chen, X., Wang, X., & Lu, X. (2023, June). Macrocyclizing DNA-Linked Peptides via Three-Component Cyclization and Photoinduced Chemistry. *Organic letters*.

[31]. Bartholomä, M. D., Ouellette, W., & Zubieta, J. (2009, January). 2-(3-[(2R,4S,5R)-4-Hydroxy-5-hydroxy-methyl-2,3,4,5-tetra-hydro-furan-2-yl]-5-methyl-2,6-dioxo-1,2,3,6-tetra-hydro-pyrimidin-1-ylmeth-yl)isoindoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 65*(Pt 2), o432-3.

[32]. Benramdane, S., De Loose, J., Beyens, O., Van Rymenant, Y., Vliegen, G., Augustyns, K., et al. (2022, August). Vildagliptin-Derived Dipeptidyl Peptidase 9 (DPP9) Inhibitors: Identification of a DPP8/9-Specific Lead. *ChemMedChem, 17*(15), e202200097.

[33]. Bhatti, M. H., Yunus, U., Saeed, S., Shah, S. R., & Wong, W.-T. (2011, August). catena-Poly[[diaqua-calcium]bis-[μ-2-(1,3-dioxoisoindolin-2-yl)acetato]-κO,O':O;κO:O,O']. *Acta crystallographica. Section E, Structure reports online, 67*(Pt 8), m1102-3.

[34]. Bielawski, K., Leszczyńska, K., Kałuża, Z., Bielawska, A., Michalak, O., Daniluk, T., et al. (2017). Synthesis and antimicrobial activity of chiral quaternary N-spiro ammonium bromides with 3',4'-dihydro-1'H-spiro[isoindoline-2,2'-isoquinoline] skeleton. *Drug design, development and therapy, 11*, 2015-2028.

[35]. Boobalan, M. s., Amaladasan, M., Ramalingam, S., Tamilvendan, D., Venkatesa Prabhu, G., & Bououdina, M. (2015, February). First principles and DFT supported investigations on vibrational spectra and electronic structure of 2-((phenylamino)methyl)isoindoline-1,3-dione–an antioxidant active Mannich base. *Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy, 137*, 962-78.

[36]. Braun, T. S., Widder, P., Osswald, U., Groß, L., Williams, L., Schmidt, M., et al. (2020, April). Isoindoline-Based Nitroxides as Bioresistant Spin Labels for Protein Labeling through Cysteines and Alkyne-Bearing Noncanonical Amino Acids. *Chembiochem : a European journal of chemical biology, 21*(7), 958-962.

[37]. Brześkiewicz, J., & Loska, R. (2023, February). Synthesis of Isoindole N-Oxides by Palladium-Catalyzed C-H Functionalization of Aldonitrones. *The Journal of organic chemistry, 88*(4), 2385-2392.

[38]. Bum-Erdene, K., Yeh, I.-J., Gonzalez-Gutierrez, G., Ghozayel, M. K., Pollok, K., & Meroueh, S. O. (2023, January). Small-Molecule Cyanamide Pan-TEAD·YAP1 Covalent Antagonists. *Journal of medicinal chemistry, 66*(1), 266-284.

[39]. Buongiorno, D., & Straganz, G. D. (2013, January). Structure and function of atypically coordinated enzymatic mononuclear non-heme-Fe(II) centers. *Structure and function of atypically coordinated enzymatic mononuclear non-heme-Fe(II) centers., 257(2)*, 541-563. Switzerland.

[40]. Büyükgüngör, O., & Odabaşoğlu, M. (2008, April). 5,6-Dichloro-2-(2-fluoro-phen-yl)iso-indoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 64*(Pt 5), o882.

[41]. Büyükgüngör, O., & Odabaşoğlu, M. (2008, April). 5,6-Dichloro-2-(3-methoxy-phen-yl)isoindoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 64*(Pt 5), o881.

[42]. Cheng, K. T., & Katsifis, A. (2004). 2-(2-(4-(4-[(123)I]Iodobenzyl)piperazin-1-yl)-2-oxoethyl)isoindoline-1,3-dione.*2-(2-(4-(4-[(123)I]Iodobenzyl)piperazin-1-yl)-2-oxoethyl)isoindoline-1,3-dione.* Bethesda (MD).

[43]. Cheng, P.-F., Wang, C.-J., & Wang, Y.-X. (2009, October). 2-(3-Bromo-prop-yl)isoindoline-1,3-dione. *Acta crystallographica. Section E, Structure reports online, 65*(Pt 11), o2646.

[44]. Chia, T. S., Kwong, H. C., Sim, A. J., Ng, W. Z., Wong, Q. A., Chidan Kumar, C. S., et al. (2019, January). Conformational dimorphism of 2,2'-methyl-enebis(isoindoline-1,3-dione). *Acta crystallographica. Section E, Crystallographic communications, 75*(Pt 1), 49-52.

[45]. Chiba, S., Nishiyama, T., & Yamada, Y. (2009, March). The antinociceptive effects and pharmacological properties of JM-1232(-): a novel isoindoline derivative. *Anesthesia and analgesia, 108*(3), 1008-14.

[46]. Zhang, Zuo-Peng / Zhong, Ye / Han, Zhen-Bin / Zhou, Lin / Su, Hua-Sheng / Wang, Jian / Liu, Yang / Cheng, Mao-Sheng Synthesis, Molecular Docking Analysis and Biological Evaluations of Saccharide-Modified Thiadiazole Sulfonamide Derivatives 2021-05 International Journal of Molecular Sciences , Vol. 22, No. 11