Jonnala.Sandhya et al /J. Pharm. Sci. & Res. Vol. 11(6), 2019, 2247-2253

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Microwave-Assisted Synthesis, Biological Evaluation and QSAR Studies of Novel Chalcone Derivatives

Jonnala.Sandhya[a,c], Bhasker Nameta[a,b], Murthy Chavali[a,d], T.Maneshwar[e] and B.V. Subba Reddy[f]

[a] *Division of Chemistry, Department of Sciences & Humanities, Vignan's Foundation for Science, Technology and Research , Vadlamudi, Guntur 522 213, Andhra Pradesh, India*
[b] *Department of Sciences and Humanities, Guru Nanak Institution of Technical Campus (JNTU), Hyderabad, Telangana, India*
[c] *Department of Sciences and Humanities, Vaageswari College of Engineering, Karimnagar – 505481*
[d] *Shree Velagapudi Ramakrishna Memorial College (SVRMC; Autonomous), Nagaram, Guntur 544 268, Andhra Pradesh, India*
[e] *Department of Pharmaceutical Chemistry, Department of Pharmaceutics, Samskruti College of Pharmacy, Kondapur, Telangana, India.*
[f] *Centre for Semiochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad – 500001, India.*

Abstract:

Novel Chalcones is considered as an important chemical for the synthesis of various physiological significance and pharmacological utilized molecules. Traditionally, chalcones are prepared by Claisen-Schmidt condensation of equimolar concentrations of arylaldehydes and acetophenones which are generally base catalyzed. The structures of the newly synthesized compounds (**3a-3t**) were elucidated by IR, 1H-NMR, Mass spectroscopy. All the synthesized compounds (**3a-3t**) screened for their anti-fungal activity and QSAR analysis was applied to a data set of 20 obtained Novel Chalcones derivatives and the best model described a strongly correlation between the anti-fungal activity and molecular descriptors as refractivity (MR), Ovality, HOMO energy (HE), LUMO energy (LE), partition coefficient (CLogP, LogP, Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded area (CSEV). All the parameters showed significant correlation with biological activity($r < 0.8$), but the molar refractivity exhibited best correlation ($r > 0.9$) of high statistical significance > 93.52%. The statistical quality of the resulting models depicted in Eqs. (1-4) is determined by r^2 ($r^2 > 0.9$). Calculated parameters and correlation matrix needed for MRA (Multiple Regression Analysis).

Keywords: Chalcones, Claisen-Schmidt condensation, Antifungal activity, QSAR; Multilinear-regression.

1. INTRODUCTION

Green chemistry is a new and rapidly emerging field of chemistry. Its growing importance is in utilization of the maximum possible resources in such a way that, there is negligible or minimum production of chemical waste. It is one of the best alternatives for traditional chemical synthesis processes. By applying the green synthesis method, we can not only avoid the use of hazardous, toxic solvents, but also the formation of by-products is avoided. Thus, they are perfectly amenable toautomation for combinatorial synthesis (Domling et al 2006). In 1986, Gedye and Giguere reported for the first time that organic reactions could be conducted very rapidly under microwave irradiation.

Schiff bases are aldehyde or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. They are widely used for industrial purposes and also exhibit a broad range of biological activities. They have been reported in their biological properties, such as, antibacterial, antifungal activities (Williams et al 1972; Campos et al 1999; Sari et al 2003; Verma et al 2004). Isatin is considered as important class of bioactive compounds exhibiting caspase (Chu.W et al 2009) inhibitor antibacterial and antiproliferative activity (Chu. W et al). Schiff bases of isatin analogous have anti smallpox (Pairing. C.M et al 2005) and GAL3 receptor antagonist capabilities (Konkelet. M. J et al 2006). Isatin derivatives reported to show antiviral (Jarrahpouret.A et al 2007), antiinflammatory, analgesic (Sharaf.O.A et al 2009), and anticonvulsant activities (Verma. M et al 2004). Isatin-β-thiosemicarbazone derivatives were found to demonstrate a range of chemotherapeutic activities (Teitz.Y et al 2006).

Chalcones are abundantly present in nature from ferns to higher plants (Star and Marby, 1971). They are aromatic compounds with an unsaturated side chain and are often cytotoxic in vitro (Dhar, 1981). Chalcones have also been reported to be antiinflammatory, analgesic and antipyretic (Satyanarayana and Rao, 1993). Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be antimutagenic (Torigoo et al., 1983). Chalcones are 1,3-diphenyl-2-propene-1-one (Nowakowska, 2007 and Maayan et al., 2005), in which two aromatic rings are linked by a three carbon a, b-unsaturated carbonyl system. These are abundant in edible plants and are considered to be the precursors of flavonoids and isoflavonoids. Chalcones are synthesized by Claisen–Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base catalysed or acid catalysed reactions followed by dehydration. Chalcone is a common natural pigment and one of the important intermediates in the biosynthesis of flavonoids. Synthetic and naturally occurring chalcones have been extensively studied and developed as one of the pharmaceutically important molecules. Chalcone derivatives are screened for their anti-inflammatory activity (Kim et al., 2007), chemo preventive activity (Shen Jeu et al., 2005), cardiovascular

disease (Liming et al., 2003), anticancer activity (Francesco et al., 2007), cytotoxic activity, antiprolifirative activity (Ducki et al., 1998), antimalarial activity (Chen et al., 1994), antiviral activity (Onyilagha et al., 1997) and anti-HIV activity (Xu et al., 2000). Therefore, in the present investigation it has been considered worthwhile to synthesize some new chalcone derivatives by conventional and microwave irradiation method.

In the present study, we have demonstrated the ability of an unusual class of synthetic molecules containing a pair of basic moieties like Indole and Benzothiazole as different pharmacological active agents. Microwave assisted synthesis for (3a–3o) were employed in solvent-free conditions, the reaction time required was limited to an average of less than 10 min. Pharmacological evaluation of the molecules reveals that compounds 3b, 3c and 3o exhibited antifungal activity nearly similar to the standard.

2. EXPERIMENTAL SECTION

2.1. Materials

The all chemicals and reagents used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Merck, Reach chem, S.D– Fine Chem. Ltd, and Sigma. The techniques employed for the characterization of the synthesized compounds were IR, ^{1}H & ^{13}C-NMR and Mass spectral analysis. 1H NMR spectra were recorded at 500 MHz and 400 MHz and ^{13}C-NMR at 125 MHz, 100 MHz and 75MHz. For ^{1}H-NMR, tetramethylsilane (TMS) was used as internal standard (δ = 0). Low-resolution MS and HRMS data were obtained using ESI ionization. IR spectra were recorded on FT-IR spectrometer (KBr) and reported in reciprocal centimeters (cm-1).

2.2. General procedure

2.2.1.Synthesis of 3-(benzo[d]thiazol-2-ylimino)-indolin-2-one (1a-1b): A mixture of 2-Amino benzothiazole (0.01mol) and corresponding isatin derivative (0.01mol) was prepared in ethanol (10 mL, containing 0.5 mL of acetic acid) in a microwave process vial (30 mL). Then the mixture was subjected to microwave irradiation at 130 W for 10min. By giving a short interval for cooling and to avoid solvent evaporation. After completion of the reaction monitored by TLC by using ethyl acetate/n-hexane, 7:3. Then flask was cooled in ice water. It was then diluted with ice-cold water. The schiff bases formed was filtered, dried and crystallized from Ethanol.

2.2.2. Synthesis of 1-acetyl-3-(benzo[d]thiazol-2-ylimino)-indolin-2-one (2a-2b): Isatin (1a-1b) (1.0 mmol) was dissolved in DMF (5 ml), and K_2CO_3 (1.3 mmol) was added. The mixture was stirred under room temperature until isatin anion was obtained and hydrogen was removed. Acetyl Chloride (4.0 mmol) was added to the reaction mixture. The reaction was subjected to under microwave irradiation for 15 minutes, at 300 W. Then the reaction mixtures were cooled overnight and the precipitates were formed in ice water. Further it was purified by recrystallization by ethanol.

2.2.3. General procedure for the synthesis of 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one (3a-3o): An equimolar mixture of compound (2a-2b) (0.01mol) and corresponding Aldehyde derivative (0.01mol) dissolved in minimum amount of rectified spirit and NaOH (40%) were placed in a conical flask. The conical flask was covered with a funnel and then the flask was taken in a domestic microwave oven. The reaction mixture was irradiated under 160-320W microwave irradiation for 60-120 sec. The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate, 7:3) after every 30 sec. The reaction mixture was cooled and the obtained solid was recrystallized from ethyl acetate and n-hexane solvent mixture.

2.2.3.1. 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one (3a): Mol. formula: $C_{24}H_{15}N_3O_2S$, Microwave irradiation yield 73%, IR (ν cm−1): 3088 (C-H *Str*, Ar), 2905(C–H *Str*, Aliphatic), 1701(C=O *Str*, Indole), 1671(C=O *Str*, Acryloyl), 1586 (CH=CH *Str*), 1539 (C=N *Str*), 1473 (C=C *Str*, Ar), 761 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.97 (d, 1H, -CO=H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48 (d, 2H, Ar-H), 7.47-7.43 (t, 2H, Ar-H), 7.33 (d, 1H, =CH-Ar), 6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 3H, Ar-H); Mass (ESI-MS): m/z 409(M), 410(M + 1, 100%).

2.2.3.2. 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-chlorophenyl) acryloyl) indolin-2-one (3b): Mol. formula: $C_{24}H_{14}ClN_3O_2S$, Microwave irradiation yield 82%, IR (ν cm−1): 3096 (C-H *Str*, Ar), 2960(C–H *Str*, Aliphatic), 1710(C=O *Str*, Indole), 1660(C=O *Str*, Acryloyl), 1576 (CH=CH *Str*), 1514 (C=N *Str*), 1434 (C=C *Str*, Ar), 846 (Ar-Cl *Str*), 758 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.15-8.11 (d, 2H, Ar-H), 8.09-8.05 (d, 2H, Ar-H), 8.01 (d, 1H, -CO=H) 7.94-7.90 (d, 2H, Ar-H), 7.89-7.84 (d, 2H, Ar-H), 7.84 (d, 1H, =CH-Ar), 7.80-7.67 (t, 2H, Ar-H), 7.14-7.09 (t, 2H, Ar-H); Mass (ESI-MS): m/z 443(M), 444(M + 1, 100%).

2.2.3.3. 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-nitrophenyl) acryloyl) indolin-2-one (3c): Mol. formula: $C_{24}H_{14}N_4O_4S$, Microwave irradiation yield 80%, IR (ν cm−1): 3096 (C-H *Str*, Ar), 2951(C–H *Str*, Aliphatic), 1746(C=O *Str*, Indole), 1667(C=O *Str*, Acryloyl), 1554 (CH=CH *Str*), 1514 (C=N *Str*), 1474 (Ar-NO_2 *Str*), 1434 (C=C *Str*, Ar), 799 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.35 (d, 1H, -CO=H), 8.06-8.04 (d, 2H, Ar-H), 7.94-7.92 (d, 2H, Ar-H), 7.92 (d, 1H, =CH-Ar), 7.82-7.81 (d, 2H, Ar-H), 7.77-7.75 (d, 2H, Ar-H), 7.17-7.14 (t, 2H, Ar-H), 6.88-6.86 (t, 2H, Ar-H); Mass (ESI-MS): m/z 454(M), 455(M + 1, 100%).

2.2.3.4. 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4,4,-dimethl amino phenyl) acryloyl) indolin- 2-one (3d): Mol. formula: $C_{26}H_{20}N_4O_2S$, Microwave irradiation yield 70%, IR (ν cm−1): 3086 (C-H *Str*, Ar), 2970,2 905(C–H *Str*, Aliphatic), 1717(C=O *Str*, Indole), 1683(C=O *Str*, Acryloyl), 1555 (CH=CH *Str*), 1520 (C=N *Str*), 1432 (C=C *Str*, Ar), 718 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.97 (d, 1H, -CO=H), 7.89-7.84 (d, 2H, Ar-H), 7.79-7.78 (d, 2H, Ar-H), 7.69-7.68 (d, 2H, Ar-H), 7.60-7.59 (d, 2H, Ar-H), 7.58-7.51(t, 2H, Ar-H), 7.49-7.48 (t, 2H, Ar-

H), 7.14 (d, 1H, =CH-Ar), 2.52-2.50(s, 6H, -N(CH_3)$_2$. Mass (ESI-MS): m/z 452(M), 453(M + 1, 100%).

2.2.3.5.3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methoxyphenyl) acryloyl) indolin-2-one (3e): Mol. formula: $C_{25}H_{17}N_3O_4S$, Microwave irradiation yield 78%, IR (ν cm−1): 3018 (C-H *Str*, Ar), 2987, 2898(C–H *Str*, Aliphatic), 1705(C=O *Str*, Indole), 1676(C=O *Str*, Acryloyl), 1540(CH=CH *Str*), 1506 (C=N *Str*), 1459 (C=C *Str*, Ar), 740 (C-S-C *Str*). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.97 (d, 1H, -CO=H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48 (d, 2H, Ar-H), 7.47-7.43 (t, 2H, Ar-H), 7.33 (d, 1H, =CH-Ar), 6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 1H, Ar-H); Mass (ESI-MS): m/z 439(M), 440(M + 1, 100%).

2.2.3.6.3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methylphenyl) acryloyl) indolin-2-one (3f): Mol. formula: $C_{25}H_{17}N_3O_2S$, Microwave irradiation yield 82%, IR (ν cm−1): 3034(C-H *Str*, Ar), 2945, 2915(C–H *Str*, Aliphatic), 1723(C=O *Str*, Indole), 1680(C=O *Str*, Acryloyl), 1582 (CH=CH *Str*), 1523 (C=N *Str*), 1440 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.02 (d, 1H, -CO=H), 7.99-7.86 (d, 2H, Ar-H), 7.75-7.64 (d, 2H, Ar-H), 7.56-7.32 (d, 2H, Ar-H), 7.03-6.90 (t, 2H, Ar-H), 6.82 (d, 1H, =CH-Ar), 6.76 (t, 2H, Ar-H), 6.46-6.35 (t, 2H, Ar-H), 2.02(s, 3H, -CH_3); Mass (ESI-MS): m/z 423(M), 424(M + 1, 100%).

2.2.3.7.3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-hydroxyphenyl) acryloyl) indolin-2-one (3g): Mol. formula: $C_{24}H_{15}N_3O_3S$, Microwave irradiation yield 81%, IR (ν cm−1): 3540 (-OH *Str*), 3023 (C-H *Str*, Ar), 2934, 2912(C–H *Str*, Aliphatic), 1713(C=O *Str*, Indole), 1682(C=O *Str*, Acryloyl), 1565 (CH=CH *Str*), 1523 (C=N *Str*), 1443 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.12 (d, 1H, -CO=H), 7.99-7.83 (d, 2H, Ar-H), 7.76-7.56 (d, 2H, Ar-H), 7.50-7.41 (d, 2H, Ar-H), 7.38-7.02 (t, 2H, Ar-H), 7.00 (d, 1H, =CH-Ar), 6.92 (t, 2H, Ar-H), 6.6.87-6.54 (t, 1H, Ar-H), 5.06 (s, 1H, Ar-OH); Mass (ESI-MS): m/z 425(M), 426(M + 1, 100%).

2.2.3.8. 3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(3,4,5-trimethoxyphenyl) acryloyl) indolin-2-one (3h): Mol. formula: $C_{27}H_{21}N_3O_5S$, Microwave irradiation yield 84%, IR (ν cm−1): 3092 (C-H *Str*, Ar), 2925(C–H *Str*, Aliphatic), 1725(C=O *Str*, Indole), 1684(C=O *Str*, Acryloyl), 1583 (CH=CH *Str*), 1546 (C=N *Str*), 1448 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.92 (d, 1H, -CO=H), 7.86-7.60 (d, 2H, Ar-H), 7.73-7.43 (d, 2H, Ar-H), 7.38-7.30 (d, 2H, Ar-H), 7.24-7.12 (t, 2H, Ar-H), 7.20 (d, 1H, =CH-Ar), 6.56-6.23 (t, 2H, Ar-H); 3.68-3.45 (s, 9H, -OCH_3) Mass (ESI-MS): m/z 499(M), 500(M + 1, 100%).

2.2.3.9. 3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(3,4-dimethoxyphenyl) acryloyl) indolin-2-one (3i): Mol. formula: $C_{27}H_{21}N_3O_4S$, Microwave irradiation yield 86%, IR (ν cm−1): 3052 (C-H *Str*, Ar), 2934, 2916, 2901 (C–H *Str*, Aliphatic), 1726(C=O *Str*, Indole), 1680 (C=O *Str*, Acryloyl), 1572 (CH=CH *Str*), 1530 (C=N *Str*), 1454 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.03 (d, 1H, -CO=H), 7.98 (s, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.42-7.29 (d, 2H, Ar-H), 7.13-7.02 (d, 2H, Ar-H), 6.93 (d, 1H, =CH-Ar), 6.58 (d, 2H, Ar-H), 6.20-6.10 (t, 2H, Ar-H), 3.54-3.50 (s, 6H, -OCH_3), 2.03-2.00 (s, 3H, -CH_3); Mass (ESI-MS): m/z 483(M), 484(M + 1, 100%).

2.2.3.10. 3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(4-methoxyphenyl) acryloyl) indolin-2-one (3j): Mol. formula: $C_{26}H_{19}N_3O_3S$, Microwave irradiation yield 79%, IR (ν cm−1): 3076 (C-H *Str*, Ar), 2965, 2904 (C–H *Str*, Aliphatic), 1717 (C=O *Str*, Indole), 1684 (C=O *Str*, Acryloyl), 1565 (CH=CH *Str*), 1523 (C=N *Str*), 1428 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.13 (d, 1H, -CO=H), 8.03(s, 1H, Ar-H), 7.86-7.80 (d, 2H, Ar-H), 7.76-7.67 (d, 2H, Ar-H), 7.50-7.38 (d, 2H, Ar-H), 7.29-7.03 (d, 2H, Ar-H), 6.93 (d, 1H, =CH-Ar), 6.20-6.10 (t, 2H, Ar-H), 3.58-3.50(s, 3H, -OCH_3), 2.18-2.10 (s, 3H, -CH_3); Mass (ESI-MS): m/z 453(M), 454(M + 1, 100%).

2.2.3.11. 3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(4-methylphenyl) acryloyl) indolin-2-one (3k): Mol. formula: $C_{26}H_{19}N_3O_2S$, Microwave irradiation yield 78%, IR (ν cm−1): 3018 (C-H *Str*, Ar), 2938, 2928, 2907(C–H *Str*, Aliphatic), 1734 (C=O *Str*, Indole), 1689 (C=O *Str*, Acryloyl), 1563 (CH=CH *Str*), 1523 (C=N *Str*), 1440 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.00 (d, 1H, -CO=H), 7.99(s, 1H, Ar-H), 7.92-7.85 (d, 2H, Ar-H), 7.74-7.46 (d, 2H, Ar-H), 7.32-7.20 (d, 2H, Ar-H), 7.19-6.99 (d, 2H, Ar-H), 6.86 (d, 1H, =CH-Ar), 6.65-6.54 (t, 2H, Ar-H), 2.23-2.13 (s, 6H, -CH_3); Mass (ESI-MS): m/z 437(M), 438(M + 1, 100%).

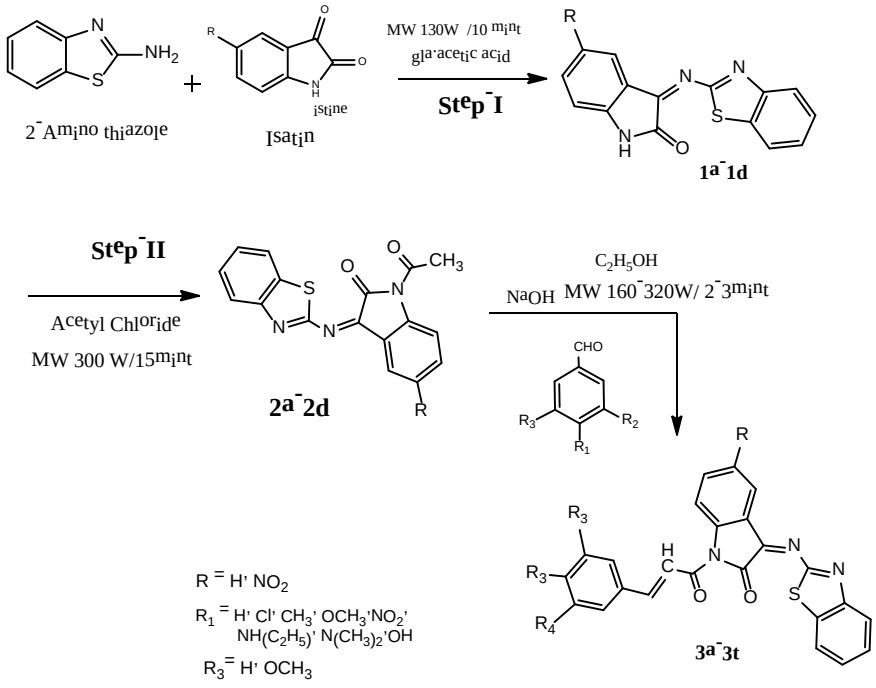
2.2.3.12. 3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(4-hydroxyphenyl) acryloyl) indolin- 2-one (3l): Mol. formula: $C_{25}H_{16}N_3O_3S$, Microwave irradiation yield 69%, IR (ν cm−1): 3503(-OH *Str*), 3064 (C-H *Str*, Ar), 2978, 2943(C–H *Str*, Aliphatic), 1723(C=O *Str*, Indole), 1683(C=O *Str*, Acryloyl), 1585 (CH=CH *Str*), 1545 (C=N *Str*), 1428 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 7.95 (d, 1H, -CO=H), 7.78-7.64 (d, 2H, Ar-H), 7.62-7.48 (d, 2H, Ar-H), 7.43-7.30 (d, 2H, Ar-H), 7.28-7.14 (t, 2H, Ar-H), 7.02 (d, 1H, =CH-Ar), 6.49 (t, 2H, Ar-H), 6.20-6.10 (t, 1H, Ar-H), 5.34(s, Ar-OH), 2.18-2.09 (s, 3H, -CH_3); Mass (ESI-MS): m/z 439(M), 440(M + 1, 100%).

2.2.3.13. 3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(4-nitrophenyl) acryloyl) indolin-2- one (3m): Mol. formula: $C_{25}H_{16}N_4O_4S$, Microwave irradiation yield 86%, IR (ν cm−1): 3075 (C-H *Str*, Ar), 2935, 2912 (C–H *Str*, Aliphatic), 1723(C=O *Str*, Indole), 1685(C=O *Str*, Acryloyl), 1632(NO_2 *Str*), 1586 (CH=CH *Str*), 1532 (C=N *Str*), 1456 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.12 (d, 1H, -CO=H), 7.84-7.70 (d, 2H, Ar-H), 7.68-7.43 (d, 2H, Ar-H), 7.40-7.34 (d, 2H, Ar-H), 7.28-7.19 (t, 2H, Ar-H), 7.03 (d, 1H, =CH-Ar), 6.86 (t, 2H, Ar-H), 6.48-6.32 (t, 1H, Ar-H), 2.38-2.12 (s, 3H, -CH_3); Mass (ESI-MS): m/z 468(M), 469(M + 1, 100%).

2.2.3.14.3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(4,4-dimethylamino-phenyl) acryloyl) indolin-2-one (3n): Mol. formula: $C_{27}H_{22}N_4O_2S$, Microwave irradiation yield 72%, IR (ν cm−1): 3045 (C-H *Str*, Ar), 2926, 2901(C–H *Str*, Aliphatic), 1724(C=O *Str*, Indole), 1685(C=O *Str*, Acryloyl), 1582 (CH=CH *Str*), 1523 (C=N *Str*), 1443 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.02 (d, 1H, -CO=H), 7.80-7.69 (d, 2H, Ar-H), 7.65-7.52 (d, 2H, Ar-H), 7.43-7.21 (d, 2H, Ar-H), 7.20-6.99 (t, 2H, Ar-H), 6.89 (d, 1H, =CH-Ar), 6.72 (t, 2H, Ar-H), 6.56-6.45 (t, 1H, Ar-

H), 2.45-2.49 (s, 6H, --N(CH_3)$_2$); Mass (ESI-MS): m/z 466(M), 467(M + 1, 100%).

2.2.3.15.3-(benzo[d]thiazol-2-ylimino)-5-methyl-1-((E)-3-(3-nitrophenyl) acryloyl) indolin-2-one (3o): Mol. formula: $C_{25}H_{16}N_4O_4S$, Microwave irradiation yield 81%, IR (ν cm−1): 3074 (C-H *Str*, Ar), 2930, 2914 (C–H *Str*, Aliphatic), 1720(C=O *Str*, Indole), 1682(C=O *Str*, Acryloyl), 1623(NO_2 *Str*), 1572 (CH=CH *Str*), 1524 (C=N *Str*), 1443 (C=C *Str*, Ar). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 8.21 (d, 1H, -CO=H), 7.94-7.82 (d, 2H, Ar-H), 7.78-7.65 (d, 2H, Ar-H), 7.54-7.48 (d, 2H, Ar-H), 7.35-7.23 (t, 2H, Ar-H), 7.12(d, 1H, =CH-Ar), 6.96(t, 2H, Ar-H), 6.54-6.43 (t, 1H, Ar-H), 2.18-2.10 (s, 3H, -CH_3); Mass (ESI-MS): m/z 468(M), 469(M + 1, 100%).



Scheme-I

Table. No.1. Antifungal activity by Zone of Inhibition (in mm)

Microorganism	Zone of Inhibition (in mm)															
	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	3m	3n	3o	Gresiofulvin
A.nagram	09	0	09	0	0	0	12	0	0	12	12	14	11	12	15*	25
P.notatum	17	15	23*	10	12	13	18	13	09	14	09	11	12	09	10	30
C.Coffeanum	0	27*	25	0	0	0	09	0	0	12	0	0	0	0	16	35
A.tivatus	12	22*	18	0	0	12	12	0	0	13	09	14	15	12	0	31

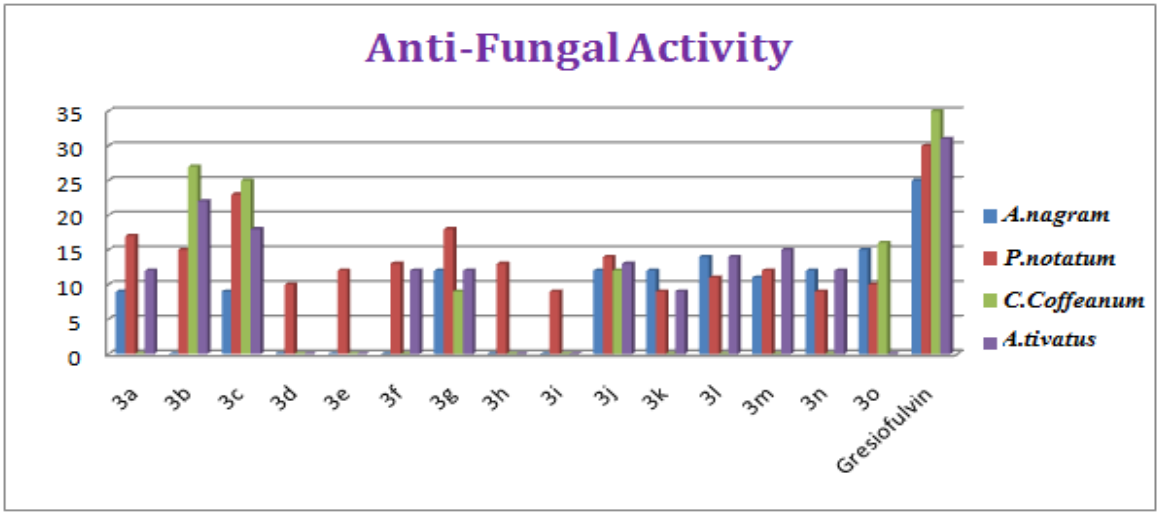


Fig 1: Graphical representation of antifungal activity of compounds (3a-3o) - Zone of Inhibition (in mm).

Table.3: Correlation matrix of calculated molecular descriptors for 3a-3o.

	log'P'	MR	HE	LE	Ovality	CLogP	CMA	CAA	CSEV
log'P'	1								
MR	0.68	1							
HE	0.02	-0.23	1						
LE	0.16	-0.02	0.67	1					
Ovality	0.20	0.73	-0.73	-0.32	1				
CLogP	0.94	0.72	-0.13	-0.03	0.29	1			
CMA	0.56	0.96	-0.32	-0.09	0.82	0.57	1		
CAA	0.51	0.92	-0.47	-0.16	0.89	0.53	0.98	1	
CSEV	0.59	0.96	-0.17	-0.00	0.72	0.59	0.98	0.94	1

3. RESULT AND DISCUSSION

3.1. Chemistry

The present work is based on the Schiff's base reaction between Indole-2,3-dione with 2-aminobenzothiazole to form 3-benzothiazole Isatin derivatives, then it can undergo acylation with acetyl chloride to give a 3-benzothiazole-N-acetyl Isatin derivatives(2a-2b). Finally these derivatives undergo the Claisen condensation reaction with different substituted Benzaldehyde with to form Novel Chalcones derivatives.

3.2. Antifungal and QSAR Studies

Antifungal activity: All the compounds (**3a–3o**) have been screened for antifungal activity using cup-plate agar diffusion method by measuring the inhibition zone in mm. Gresiofulvin (50 µg/mL) was used as a standard drug for antifungal activity. The compounds were screened for antifungal activity against *Aspergillus Niger*, *Colletotrichm coffeanum*, *Aspergillus tevatus*, *and Pencillium notatum* and in nutrient agar medium. All values are expressed as Zone of Inhibition in mm, Bore size = 6mm; *Compounds showed maximum activity against respective Fungal; Zone size 9-11 = Poor activity; Zone size 12-18 = Moderate activity, Concentration of test compounds is 50µg/ml.

QSAR analysis: A classical Hansch multivariate regression analysis using the chosen to derive QSAR equations for the data set (**Table 5**). The level of significance of each coefficient was judged by statistical procedure such as *F* test. Statistic analysis was carried out by employing the method of least square using the EASY QSAR 1.0 software, with stepwise selection and elimination procedure. For each equation several indices of best fit were considered: the regression coefficient "*r*", the standard deviation "*s*", and the measure of level of statistical significance "*F*".

GENERATED QSAR EQUATION:

Log (1/C) = 2.79 + 0.0655(MR) + 0.292 (Ovality) + 0.00124 (CMA) + -0.000647(CAA) -0.000578 (CSEV).

Table 2: Statistics of the analysis:

SSR	0.06
SSE	0.00
SST	0.07
r^2	93.52%
r^2_{adj}	89.92%
F statistics	25.98
Critical *F*	2.96

Where, SSR = Residual sum of squares, SSE = Error sum of squares, SST = Total sum of squares. The r^2 value should be definitely high for a good QSAR equation. Higher r^2 means higher fitting of the equation to the given data. Hence better predictions it will provide for new test data. High difference in r^2 and r^2_{adj} indicates weaker overall prediction. The *F* statistics of the test should be greater than Critical *F* otherwise the generated equation is inefficient.

Following high correlating descriptor pairs found:

CLogP*log'P'; CMA*MR; CAA*MR; CAA*CMA; CSEV*MR; CSEV*CMA; CSEV*CAA.

Table .4: Correlation of descriptors with activity

log'P'	0.60
MR	0.96
HE	-0.30
LE	-0.17
Ovality	0.76
CLogP	0.67
CMA	0.93
CAA	0.91
CSEV	0.92

Table.5: Percentage contribution of each descriptor to activity.

log'P'	36.53%
MR	92.55%
HE	9.11%
LE	3.06%
Ovality	57.59%
CLogP	45.41%
CMA	86.75%
CAA	82.35%
CSEV	84.90%

Correlation value ranges from -1 through 0 to +1. -1 means perfect negative correlation, 0 means no correlation at all, +1 means perfect positive correlation. The correlation value is thus a helping aid to see the trend of relatedness among descriptors and between descriptors and activity. Ideally descriptors should show high correlation with activity. High correlation among descriptors indicates that both of them essentially

represent the same feature. To be a good Predictor the descriptor should contribute >50% to the activity. The values indicated as percentage contribution are the independent r^2values of each descriptor if they were alone.

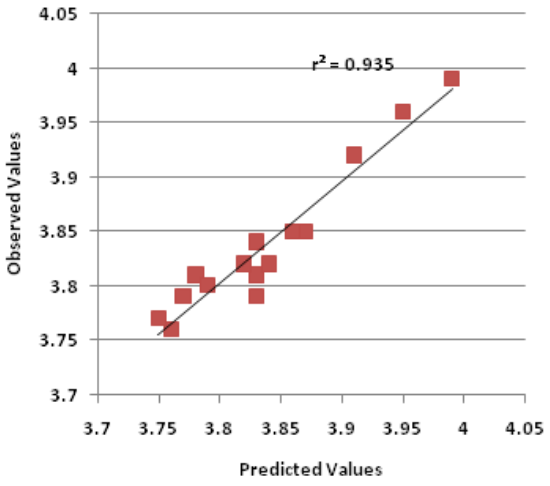


Fig.2: Graphical representation of the Observed Activity versus the Predicted activity.

The plot shows the relationship between the Observed activity and the predicted activity for the same training data generated by the equation. Thus it tests how well the equation fits the data.

Table.6: The actual and the Predicted values are listed below.

S.NO	log (1/C) Observed	log (1/C) Predicted P	RESIDUAL
1	3.83	3.81	0.02
2	3.83	3.84	-0.01
3	3.76	3.76	0
4	3.75	3.77	-0.02
5	3.78	3.81	-0.03
6	3.79	3.80	-0.04
7	3.83	3.79	0.03
8	3.82	3.82	0
9	3.77	3.79	-0.02
10	3.87	3.85	0.02
11	3.84	3.82	0
12	3.95	3.96	-0.01
13	3.91	3.92	-0.00
14	3.99	3.99	0
15	3.86	3.85	0.01

All the parameters showed significant correlation with biological activity(r < 0.8) (**Table 4**), but the molar refractivity exhibited best correlation (r > 0.9) of high statistical significance > 93.52%. The statistical quality of the resulting models depicted in Eqs. (1-4) is determined by r^2 (r^2 > 0.9). Calculated parameters and correlation matrix needed for MRA (Multiple Regression Analysis) are shown in **Table 3**.

4. CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of novel Chalcone derivatives. The yield of the synthesized compound was found to be in the range from 68-85% (Microwave). All these molecules were characterized by FT-IR, ^{1}H-NMR and Mass spectral analysis along with physical data. The synthesized compounds (**3a-3o**) were also screened for antifungal activity by measuring zone of inhibition by agar diffusion method. Gresiofulvin as standard drug. From the 2D-QSAR data in order to correlate the molecular descriptors of the synthesized compounds with antioxidant activity. The radical scavenger activities of 15 derivatives was successfully modeled through MLR using Easy QSAR 1.0 and molecular descriptors of electronic, steric and thermodynamic using Chem 3D Ultra 7.0. The QSAR obtained showed significant correlation Coefficients $\boldsymbol{r^2}$ = **0.935.**

REFERENCE:

1. Domling, A. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. *Chem. Rev.* 2006, *106*, 17–89.
2. Williams, D.R. Metals, ligands, and cancer. Chem. Rev. 1972, 72, 203-213.
3. Campos, A.; Anacona J.R.; Campos-Vallette, M.M. Synthesis and IR study of a zinc(II) complex containing a tetradentate macrocyclic Schiff base ligand: Antifungal properties. Group. Metal Chem. 1999, 22, 283-288.
4. Sari, N.; Arslan, S.; Logoglu, E.; Sakiyan, I. Antibacterial activities of some new amino acid-Schiff bases. G. U. J. Sci. 2003, 16, 283-288.
5. Verma, M.; Pandeya, S.N.; Singh, K.N.; Stabler, J.P. Anticonvulsant activity of Schiff bases of isatin derivatives. Acta Pharm. 2004, 54, 49-56.
6. Chu. W, Zhang. J, Zeng. C et al., "*N*-benzylisatin sulfonamide analogues as potent caspase-3 inhibitors: synthesis, in vitro activity, and molecular modeling studies," *Journal of Medicinal Chemistry*, vol. 48, no. 24, pp. 7637–7647, 2005.
7. Chu.W, Rothfuss. J, Chu. Y, Zhoud.D and R. H. Mach, "Synthesis and *in vitro* evaluation of sulfonamide isatin Michael acceptors as small molecule inhibitors of caspase-6," *Journal of Medicinal Chemistry*, vol. 52, no. 8, pp. 2188–2191, 2009.
8. Chohan. Z. H, Pervez. H, Rauf. A, Khan, and C. T. Supuran, "Isatin-derived antibacterial and antifungal compounds and their transition metal complexes," *Journal of Enzyme Inhibition and Medicinal Chemistry*, vol. 19, no. 5, pp. 417–423, 2004.
9. Pirrung. C.M, Pansare.S, Das Sarma, K.V, Keith. K. A. and Kern. E. R, "Combinatorial optimization of isatin-β thiosemicarbazones as anti-poxvirus agents," *Journal of Medicinal Chemistry*, vol. 48, no. 8, pp. 3045–3050, 2005.
10. M. J. Konkel, B. Lagu, L. W. Boteju et al., "3-Arylimino- 2-indolones are potent and selective galanin GAL3 receptor antagonists," *Journal of Medicinal Chemistry*, vol. 49, no. 13, pp. 3757–3758, 2006.
11. A. Jarrahpour, D. Khalili, E. De Clercq, C. Salmi, and J. M. Brunel, "Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new *bis*-Schiff bases of isatin and their derivatives," *Molecules*, vol. 12, no. 8, pp. 1720–1730, 2007.
12. O. A. Sharaf, "Some pharmacological activities of new substituted pyrolloindoles, indolothiazepine and azole derivatives," *Bulletin of Faculty of Pharmacy*, vol. 35, pp. 79–82, 1997.
13. M. Verma, S. N. Pandeya, K. N. Singh, and J. P. Stables, "Anticonvulsant activity of Schiff bases of isatin derivatives," *Acta Pharmaceutica*, vol. 54, no. 1, pp. 49–56, 2004.
14. Y. Teitz, D. Ronen, A. Vansover, T. Stematsky, and J. L. Riggs, "Inhibition of human immunodeficiency virus by *N*-methyl satin-β4:4-diethylthiosemicarbazone and *N*-allylisatin- β-4':4'-

diallythiosemicarbazone," *Antiviral Research*, vol. no. 4, pp. 305–314, 1994.
15. Star, A.W., Marby, T.J., 1971. Flavanoid front exudates from two Jamaican ferns, Pityrogrammu tartarea and P Calomelanos. Phytochemistry 10, 2812–2817.
16. Dhar, D.N., 1981. The Chemistry of Chalcones and Related Compounds. Wiley, New York, pp. 213.
17. Satyanarayana, K., Rao, M.N.A., 1993. Anti-inflammatory, analgesic and anti-pyretic activities of 3-(4-(3-(4-dimethylaminophenyl)-1-oxo-2-propenyl) phenyl) sydnone. Indian Drugs 30, 313–318.
18. Torigoo, T., Arisawa, M., Iloch, S., Fujiu, M., Mayuyama, H.B., 1983. Anti-mutagenic chalcones: antagonizing the mutagenicity of benzo (a) pyrene in Salmonella ty- phymurrum. Biochem. Biophys. Res. Commun 112, 833–842.
19. Nowakowska, Z., 2007. Eur. J. Med. Chem 42, 125.
20. Maayan, S., Ohad, N., Soliman, K., 2005. Bioorg. Med. Chem 13 (2), 433.
21. Kim, Young Hoon, Kim, Jeongsoo, Park, Haeil, Kim, Hyun Pyo, 2007. Biol. Pharm. Bull. 30 (8), 1450–1455.
22. Shen Jeu, W., Cheng Tsung, L., Lo Ti, T., Jing Ru, W., Hrogn Huey, K., Jih Pyang, W., Chun Nan, L., 2005. Eur. J. Med. Chem. 40, 103.
23. Liming, N., Kimberly, W.J., Weingarten, M., Janes, S.A., 2003. PCT Int. Appl., 411.
24. Francesco, E., Salvatore, G., Luigi, M., Massimo, C., 2007. Phytochemistry 68, 939.