SYNTHESIS OF NOVEL CHALCONE DERIVATIVES AND IT'S BIOLOGICAL ACTIVITY

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ABSTRACT

A series of some novel Chalcone derivatives ones were synthesized by condensing substituted N-acetyl Isatin with substituted aldehydes to yield the title compounds. The structures of the newly synthesized compounds (**3a-3o**) were elucidated by IR, 1H-NMR, Mass spectroscopy. All the synthesized compounds (**3a-3o**) screened for their anti-fungal activity 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 ($r^2 > 0.9$).

Keywords: Chalcones, Claisen-Schmidt condensation, Antifungal activity.

I. 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 minimumproduction of chemical waste. It is one of the best alternatives for traditional chemical synthesisprocesses[22]. 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 [1]. 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 [2-5]. Isatin is considered as important class of bioactive compounds exhibitingcaspase[6] inhibitor antibacterial and antiproliferative activity [7]. Schiff bases of isatin analogous have anti smallpox [8]and GAL3 receptor antagonist capabilities [9]. Isatin derivatives reported to show antiviral [10], antiinflammatory, analgesic [11], and anticonvulsant activities [12]. Isatin-β-thiosemicarbazone derivatives were found to demonstrate a range of chemotherapeutic activities [13].Chalcones are abundantly present in nature from ferns to higher plants [14-15]. They are aromatic compounds with an unsaturated side chain and are often cytotoxic in vitro [16]. Chalcones have also been reported to be antiinflammatory, analgesic and antipyretic [17].Some chalcones possess bactericidal, antifungaland insecticidal activity and some of their derivatives arereported to be antimutagenic [18]. Chalconesare 1,3-diphenyl-2-propene-1-one[19], in which two aromatic rings are linkedby a three carbon a, b-unsaturated carbonyl system.

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 Benzothiazoleas different pharmacological active agents. Microwaveassisted 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 ofthe molecules reveals that compounds 3b, 3c and 3o exhibitedantifungal activity nearlysimilar to the standard.

II. MATERIALS AND METHODS

Thea11 chemicalsandreagentsusedinthepresentprojectwereofARandLR grade,procuredfromAldrich,Hi-media,Merck,Reachchem, S.D– Fine Chem. Ltd, and Sigma.Thetechniquesemployedforthecharacterizationofthesynthesizedcompoundswere 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 ($\delta = 0$). 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).

a. General procedure

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.

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.

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 microwaveirradiation 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.

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(phenyl) acryloyl) indolin-2-one (3a): Appearance: white solid; m.p. 213–215°C;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%).

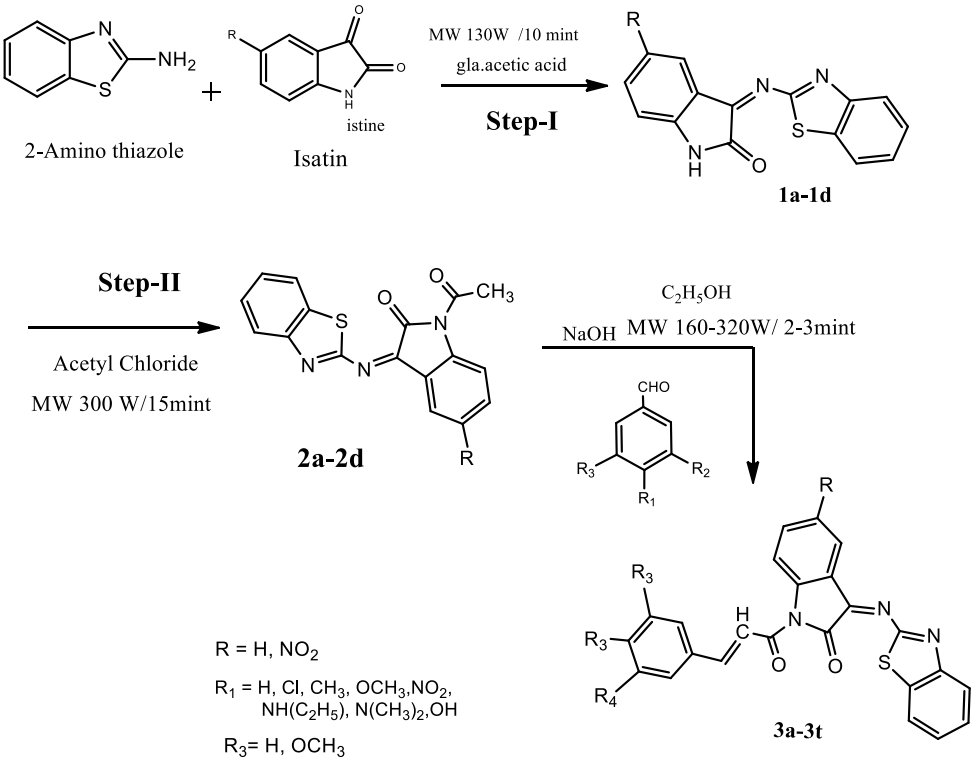
3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-chlorophenyl) acryloyl) indolin-2-one (3b): Appearance: red solid; m.p. 234–236°C, Mol. formula: $C_{24}H_{14}ClN_3O_2S$, Microwave irradiation yield 82%, IR (ν cm−1): 3096 (C-H Str, Ar), 2960(C–H Str, Aliphatic), 1710(C=O Str, Indole), 1660(C=O Str, Acryloyl), 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%).

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-nitrophenyl) acryloyl) indolin-2-one (3c): Appearance: yellow solid; m.p. 201–203°CMol. 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%).

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4,4,-dimethl amino phenyl) acryloyl) indolin-2-one (3d): Appearance: pale yellow solid; m.p. 225–227°CMol. 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%).

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methoxyphenyl) acryloyl) indolin-2-one (3e): Appearance: yellow solid; m.p. 259–261°CMol. 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%).

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methylphenyl) acryloyl) indolin-2-one (3f): Appearance: red solid; m.p. 225–227°C,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%).



Scheme-I

III. RESULT AND DISCUSSION

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 reactionwith different substituted Benzaldehyde with to form Novel Chalcones derivatives.

Biological Study

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 [3]. The compounds were screened for antifungal activity against Aspergillus Niger, Colletotrichmcoffeanum, Aspergillus tevatus, and Pencillium notatum and in nutrient agar medium.

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

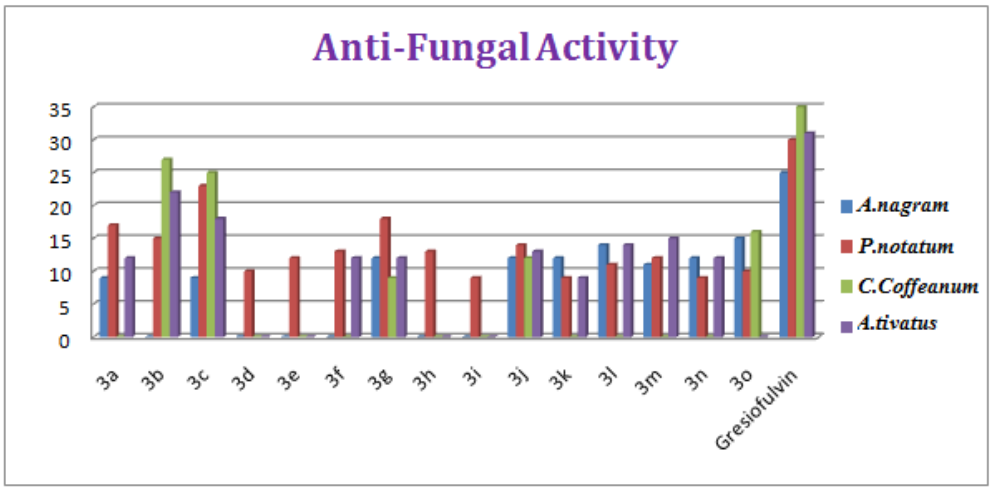


Fig 1: Graphical representation of antifungal activity of compounds (3a-3o)

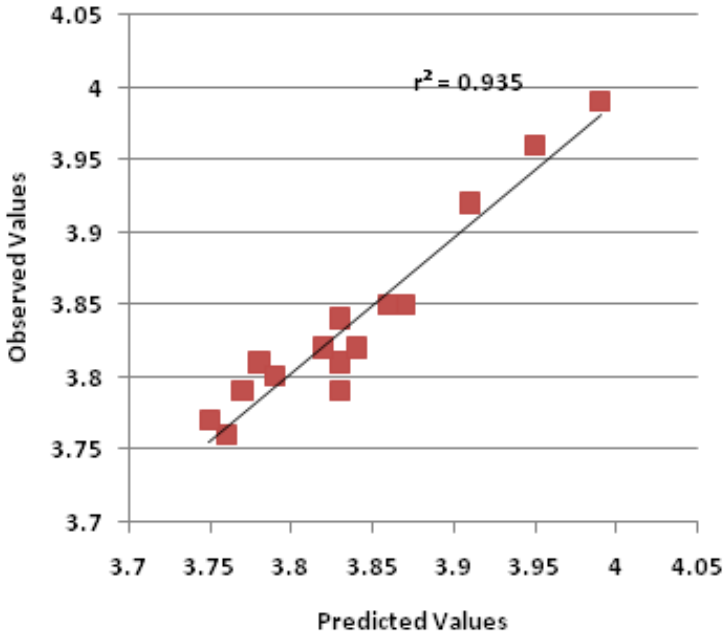


Fig.2: Graphical representation of the Observed Activity versus the Predicted activity.

IV. CONCLUSION

Theobjectiveofthepresentworkwastosynthesize,purify,characterizeandevaluate the biological activity of newly synthesized structural analogsofnovel Chalcone derivatives. Theyieldofthesynthesizedcompoundwasfoundtobeintherangefrom68-85% (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.

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