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

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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. The structures of the newly synthesized compounds (3a-3o) were elucidated by Infrared (IR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Mass spectroscopy. All the synthesized compounds (3a-3o) screened for their anti-fungal activity and QSAR analysis was applied to a data set of 15 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 ($r^2>0.9$).

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

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 [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 exhibiting caspase [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, antifungal and insecticidal activity and some of their derivatives are reported to be antimutagenic [18]. Chalcones are 1,3-diphenyl-2-propene-1-one [19], in which two aromatic rings are linked by 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 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.

MATERIALS AND METHODS

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 Infrared (IR), Proton Nuclear magnetic Resonance (^{1}H-NMR) and Carbon-13 Nulcear Magnetic Resonance (^{13}C-NMR) and Mass spectral analysis. ^{1}H-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 Fourier Transform Infrared (FT-IR) spectrometer (KBr) and reported in reciprocal centimeters (cm^{-1}).

General procedure (Scheme 1)

Synthesis of 3-(benzo[d]thiazol-2-ylimino)-indolin-2-one (1a-1b)

A mixture of 2-Amino benzothiazole (0.01 mol) and corresponding isatin derivative (0.01 mol) 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 10 min. By giving a short interval for cooling and to avoid solvent evaporation. After completion of the reaction monitored by Thin Layer Chromatography (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 min, 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) (0.01 mol) and corresponding Aldehyde derivative (0.01 mol) 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 160-320 W microwave irradiation for 60-120 s. The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate, 7: 3) after every 30 s. 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°C-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°C-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°C-203°C 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%).

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°C-227°C, 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%).

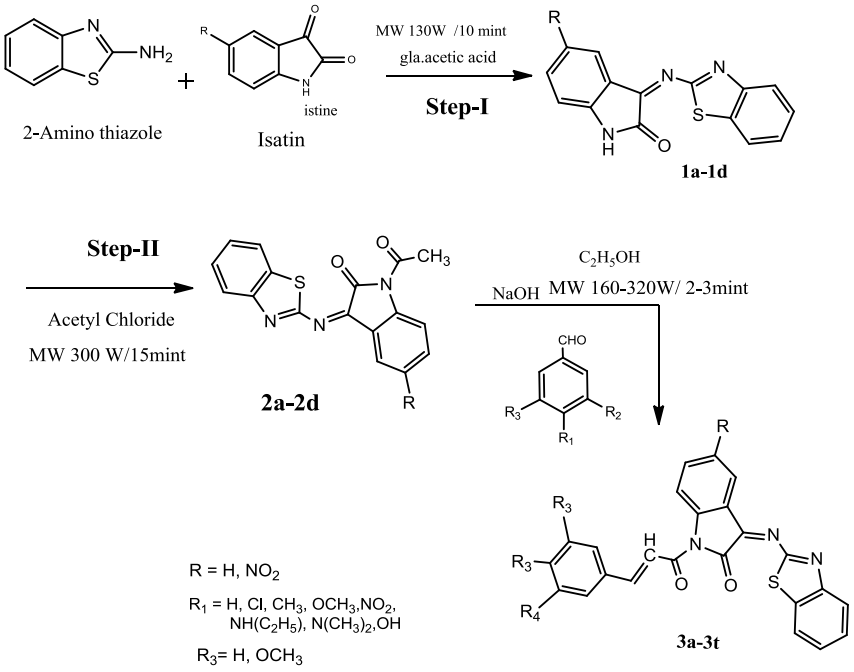
3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methoxyphenyl) acryloyl) indolin-2-one (3e)

Appearance: Yellow solid; m.p. 259°C-261°C 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%).

3-(benzo[d]thiazol-2-ylimino)-1-((E)-3-(4-methylphenyl) acryloyl) indolin-2-one (3f)

Appearance: Red solid; m.p. 225°C-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) *δδ* (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 1: General procedure for the synthesis of Compunds 3a-3t

RESULTS 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 reaction with different substituted Benzaldehyde with to form Novel Chalcones derivatives.

Antifungal and QSAR Studies

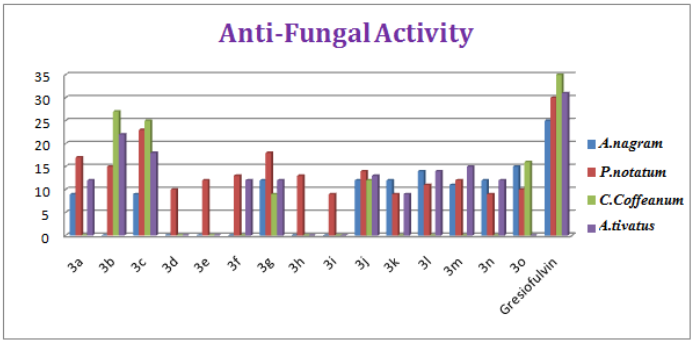
Antifungal activity

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 [20]. The compounds were screened for antifungal activity (Figure 1 and Table 1) against *Aspergillus niger, Colletotrichm coffeanum, Aspergillus tevatus, and Pencillium notatum* and in nutrient agar medium.

Table 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
Aspergillus niger	9	0	9	0	0	0	12	0	0	12	12	14	11	12	15*	25
Pencillium notatum	17	15	23*	10	12	13	18	13	9	14	9	11	12	9	10	30
Colletotrichm coffeanum	0	27*	25	0	0	0	9	0	0	12	0	0	0	0	16	35
Aspergillus tevatus	12	22*	18	0	0	12	12	0	0	13	9	14	15	12	0	31

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



QSAR analysis

A classical Hansch multivariate regression analysis using the chosen to derive QSAR equations for the data set (Table 2). 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*".

Table 2: Statistic analysis by the method of least square

SSR	0.06
SSE	0
SST	0.07
r^2	93.52%
r^2_{adj}	89.92%
***F* statistics**	25.98
Critical *F*	2.96

Generated qsar equation

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

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	0.2	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	0.72	0.59	0.98	0.94	1

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

log'P'	0.6
MR	0.96
HE	0.3
LE	0.17
Ovality	0.76
CLogP	0.67
CMA	0.93
CAA	0.91
CSEV	0.92

Table 5: Percentage contribution of each with activity 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 (Table 3) 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 (Table 4) 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 (Table 5) should contribute >50% to the activity. The values

indicated as percentage contribution are the independent r^2 values of each descriptor if they were alone.

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	3.8	-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
14	3.99	3.99	0
15	3.86	3.85	0.01

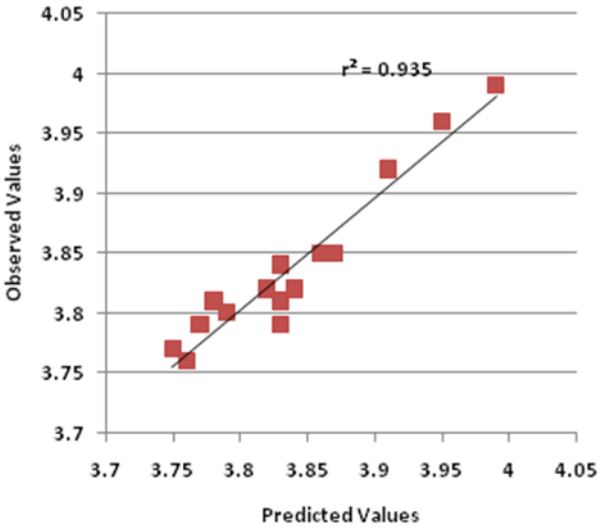


Figure 2: Graphical representation of the observed activity versus the predicted activity

The plot Figure 2 and Table 6 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. 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 Equations 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.

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 r^2=0.935.

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