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Microwave Assisted Synthesis of Heterocycles Accompanied by Antimicrobial Screening

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Abstract – ***A clean, efficient and solvent free method for the synthesis of Bis-chalcones and Pyrazoles were carried out with the help microwave irradiations and neutral alumina. The novel class of Bis-chalcones and pyrazoles were comprehended by treatment of N-phenyl succinimides with p-fluoro benzaldehyde. The cyclic imide on condensation with p-fluoro benzaldehyde furnished a series of bis chalcones and further they undergo cyclisation with hydrazine hydrate to furnish pyrazoles. This condensation could make better and easier by solvent free mechanism with the help of microwave irradiations and neutral alumina. This method furnished various advantages, such as straight forward work-up procedure, environmentally benevolent, neutral condition and high yield. All the synthesized moieties were characterized and interpreted for antimicrobial activities.***

Keywords: Green Chemistry, Clean, Solvent free, Bis-chalcones, Pyrazoles, Hydrazine hydrate.

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1. INTRODUCTION

Heterocycles with nitro moiety offers the prodigious fortune for the designing of novel and compelling medicinal drugs (Pozharskii, et. al., 1997, Katritzky, et. al., 2000).Heterocyclic compounds such as succinimides, glutarimides and their malononitriles and chalcone centered pyrazolines, pyrimidines derivatives furnish a very important lead role in the synthesis of organic compounds. The defensive antimicrobial activities (Katritzky, 1985, Kontogiorgis, et. al., 2008, Chaudhari & Rajput, 2018, Perisic-Janjic, et. al., 2013, Chaudhari & Rajput, 2016, Musso, et. al., 2003) have seen in the chalcones and cyclic imides.

Pyrazole plays very important role in the field of medicinal chemistry. Perhaps, they have been shown significant biological activities (Pekalaa, et. al., 2013, Chaudhari & Rajput, 2018, Rao, et. al., 2010, Dhivare, et. al., 2018, Ducki, et. al., 2009) like antimicrobial, antineoplastic, anti-inflammatory (Chaudhari & Rajput, 2016), antiviral etc.

Microwave supported synthesis offers the abundant benefits as assessed to traditional thermal heating method. It has very significant attributes for the SAR generation cycle due to its noteworthy advantages and reduces the duration of process. As shown in the evaluation diagram of traditional and microwave methods; succeeding discoveries are documented such as extensive conversion of end product within short duration, pure product, sophisticated, eco-friendly greener approach. Hence the microwave supported synthesis and traditional thermal reflux method has been compared for the SAR analysis as shown in the Fig. 01.

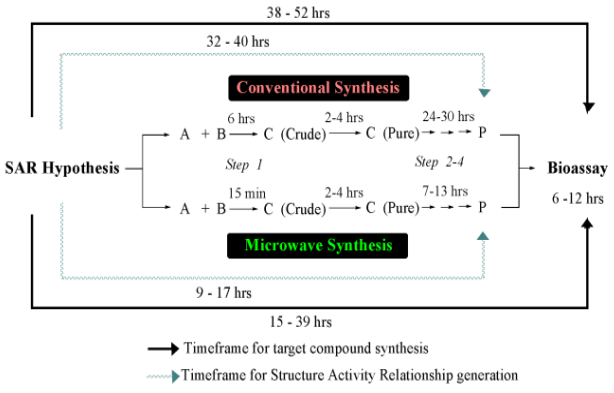


Fig 01: Structure Activity Relationship generation of target compounds

2. REVIEW OF LITERATURE

Taherpour A., (2005) synthesized cyclic imides by using microwave oven. They found rapid conversion of lactones to cyclic imides.They kept microwave at 50W irradiation mode for 5 minutes and good yield was observed when per acetic acid react with manganic chloride in presence of solvent ethyl acetate.

Boumendjel A., (2008) developed 59 chalcones and screened for the antimitotic activity on human leukemic K562 cell line. They have explained how cells were exposed to test compounds at a concentration of 10 µM for 24 h and stained with propidium iodide and analyzed by flow cytometry to determine the distribution of the total population in the different phases (G0/G1, S, and G2/M). Compounds inducing G2/M arrest equal to or higher than our reference compound, vincristine (VCR) were evaluated for the antiproliferative effect against a panel of cell lines representing different types of cancer.

Dimmock J., (1998) studied that Mannich bases of chalcones are novel cytotoxic agents whose activity is influenced by a number of physicochemical parameters including the ð, ó, and MR constants of the aryl rings and redox potentials along with other structural features revealed by X-ray crystallography and molecular modeling. Several lead molecules have been found high potency toward L1210 cells and human tumor cell lines with marked lethality to P388 cells and with a good therapeutic index when the IC50 values of P388 and Molt 4/C8 cells were compared. The absence of mutagenic properties is a further pointer that development of these compounds may lead to useful therapeutic agents.

Hafez H., (2016) have reported a novel class of compounds and these compounds were tested for their in vitro anti-cancer and anti-microbial activities. Few of the synthesized novel compounds have been showed excellent anti-microbial activity as compare to standard drugs. Also, some of them exhibited higher anti-cancer activity than the doxorubicin. It has been observed that the activities of these compounds are strongly dependent on the basic skeleton of the molecules and the nature of heterocyclic ring attached to the pyrazole unit, also the nature of the substituent at the carbohydrazide.

3. EXPERIMENTAL

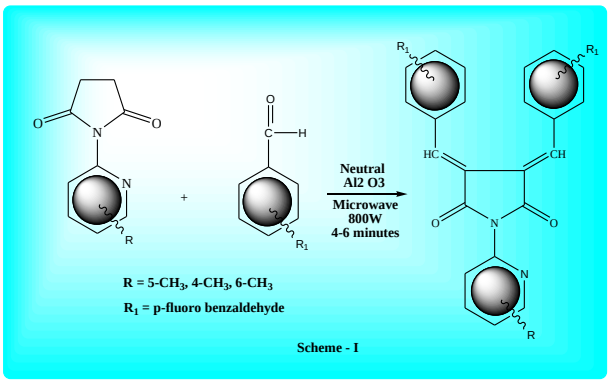
3.1 Material Methods:

Melting points were recorded in open glass capillaries and were uncorrected. The chemical structures of the obtained compounds were confirmed by spectral analyses. IR spectra in KBr pallets were obtained on Simadzu and ATR Brucker alpha FT-IR spectrophotometer.1H NMR spectra were obtained on and 500.13 MHz by Brucker spectrophotometer. The chemical shifts were reported as parts per million (ppm) with $(CH_3)_4Si$ (TMS) as an internal standard. Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), m (multiplet).The purity of compound was checked by thin layer chromatography which was performed by using pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate 7:3 proportion. Anti-microbial and Anti-fungal activities were carried out by Agar diffusion assay (Disk diffusion method, Disk size 6 mm). All the compounds (1a-f) were synthesized from the corresponding Succinic Anhydride derivatives and commercially purchased p-fluoro benzaldehyde and neutral alumina (Al_2O_3).

3.2 General Procedure of synthesis:

3.2.1 Preparation of of Bis-Chalcones (1a-c):

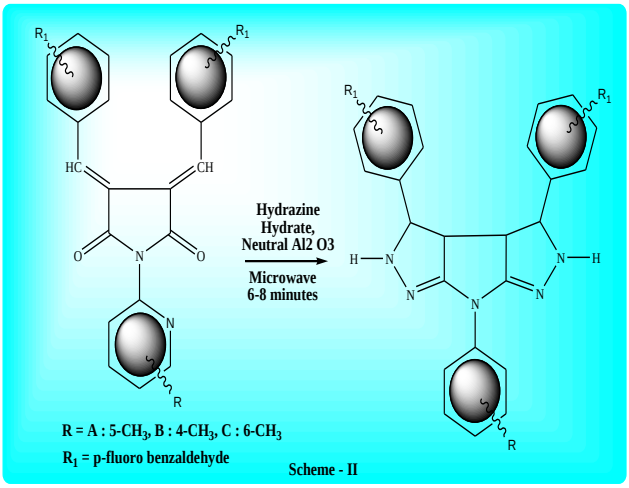
A mixture of N-phenyl succinimide derivatives (0.01mole) and p-floro benzaldehyde (0.02mole) in 1 gm of neutral Al_2O_3 were condensed with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 4-6 minutes in solvent free condition. The novel developed compounds were recrystallized from ethanol. **(Scheme–I)**.



Scheme - I

3.2.2 Preparation of of Pyrazoles (1d-f):

A mixture of bis-chalcone – 1a-c (0.01mole) and hydrazine hydrate (0.02mole) in 1 gm of neutral Al_2O_3 were condensed with the help of microwave irradiations. This mixture is maintained in microwave at 800W power for 6-8 minutes in solvent free condition. The novel developed compounds were recrystallized from ethanol. **(Scheme–II)**.



Scheme - II

3.3 Physicochemical and analytical data for compounds 1a-f:

3,4-bis((E)-4-fluorobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (1a):

$C_{24}H_{16}F_2O_2N_2$, Zinc Yellow Solid, MW: 402.39, Yield: 85.53%, MP(ºC): 280-82 ºC, Cal: C (71.64%) H (4.01%) N (6.96%); Obs: C (70.72%) H (4.16%) N (6.73%), FTIR (KBr): -C-F:1176.24; >C=C<: 1685.72; >C=O: 1720.06; aromatic ring (3-Peaks): 3197.21, 3127.93, 790.52; $-CH_3$: 2799.21; C-N (Aliphatic): 1196.71; C-N (Aromatic): 1327.67; -C-C- Stretch in a ring(2-Peaks): 1570.08, 1530.18; $-CH_3$ bend: 1425.27, 1397.32 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 7.72 (m, 2H, ethylene), 7.52-8.01 (m, 11H, aromatic), 2.18 (s, 3H, CH_3 -pyridine).

3,4-bis((E)-4-fluorobenzylidene)-1-(4-methylpyridin-2-yl)pyrrolidine-2,5-dione (1b):

$C_{24}H_{16}F_2O_2N_2$, Melon Yellow Solid, MW: 402.39, Yield: Green: 83.25%, MP(ºC): 284-86 ºC, Cal: C (71.64%) H (4.01%) N (6.96%); Obs: C (70.89%) H (4.37%) N (6.48%), FTIR (KBr): -C-F:1172.06; >C=C<: 1678.16; >C=O: 1728.92; aromatic ring (3-Peaks): 3084.82, 3010.07, 800.78; $-CH_3$: 2789.83; C-N (Aliphatic): 1211.80; C-N (Aromatic): 1307.67; -C-C- Stretch in a ring(2-Peaks): 1678.77, 1535.27; $-CH_3$ bend: 1487.35, 1307.93 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 7.83 (m, 2H, ethylene), 7.41-7.98 (m, 11H, aromatic), 2.20 (s, 3H, CH_3 -pyridine).

3,4-bis((E)-4-fluorobenzylidene)-1-(6-methylpyridin-2-yl)pyrrolidine-2,5-dione (1c):

$C_{24}H_{16}F_2O_2N_2$, Reseda Green Solid, MW: 402.39, Yield: 91.10%, MP(ºC): 184-86 ºC, Cal: C (71.64%) H (4.01%) N (6.96%); Obs: C (71.03%) H (4.47%) N (6.38%), FTIR (KBr): -C-F:1167.85; >C=C<: 1672.24; >C=O: 1732.44; aromatic ring (3-Peaks): 3089.54, 3015.17, 810.74; $-CH_3$: 2779.47; C-N (Aliphatic): 1217.25; C-N (Aromatic): 1317.94; -C-C- Stretch in a ring(2-Peaks): 1557.28, 1531.47; $-CH_3$ bend: 1440.46, 1370.95 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 7.86 (m, 2H, ethylene), 6.86-7.76 (m, 11H, aromatic), 2.49 (s, 3H, CH_3 -pyridine).

3,4-bis(4-fluorophenyl)-7-(5-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (1d):

$C_{24}H_{20}F_2N_6$, Saffron Yellow Solid, MW: 430.4, Yield: 87.68%, MP(ºC): 314-16 ºC, Cal: C (66.97%) H (4.68%) N (19.52%); Obs: C (66.10%) H (4.27%) N (19.17%), FTIR (KBr): -C-F:1175.25; -N-H: 3415.43; >C=N: 1670.23; aromatic ring (2-Peaks): 3032.71, 838.48; $-CH_3$: 2947.17; C-N (Aliphatic): 1220.80; C-N (Aromatic): 1290.73; -C-C- Stretch in a ring(2-Peaks): 1610.41, 1564.22; $-CH_3$ bend: 1445.72, 1370.65 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.17 (t, 2H, Methine), 3.08 (d, 2H, Methine), 9.95 (s, 2H,-N-H), 6.57-7.95 (m, 11H, aromatic), 2.28 (s, 3H, CH_3-pyridine).

3,4-bis(4-fluorophenyl)-7-(4-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (1e):

$C_{24}H_{20}F_2N_6$, Yellow Orange Solid, MW: 430.45, Yield: 77.52%, MP(ºC): 308-10 ºC, Cal: C (66.97%) H (4.68%) N (19.52%); Obs: C (66.03%) H (4.18%) N (19.05%), FTIR (KBr): -C-F:1169.33; -N-H: 3262.53; >C=N: 1679.69; aromatic ring (2-Peaks): 3026.78, 815.57; $-CH_3$: 2927.37; C-N (Aliphatic): 1224.43; C-N (Aromatic): 1297.14; -C-C- Stretch in a ring(2-Peaks): 1616.95, 1599.49; $-CH_3$ bend: 1461.58, 1331.88 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.26 (t, 2H, Methine), 3.80 (d, 2H, Methine), 9.88 (s, 2H,-N-H), 6.77-7.86 (m, 11H, aromatic), 2.32 (s, 3H, CH_3-pyridine).

3,4-bis(4-fluorophenyl)-7-(6-methylpyridin-2-yl)-3,3a,3b,4,5,7-hexahydro-2H-pyrrolo[2,3-c:5,4-c']dipyrazole (1f):

$C_{24}H_{20}F_2N_6$, Sulfur Yellow Solid, MW: 430.45, Yield: 63.62%, MP(ºC): 288-90 ºC, Cal: C (66.97%) H (4.68%) N (19.52%); Obs: C (66.16%) H (4.30%) N (19.95%), FTIR (KBr): -C-F:1153.58; -N-H: 3452.61; >C=N: 1628.10; aromatic ring (2-Peaks): 3014.92, 826.06; $-CH_3$: 2967.66; C-N (Aliphatic): 1222.93; C-N (Aromatic): 1293.15; -C-C- Stretch in a ring(2-Peaks): 1599.49, 1504.48; $-CH_3$ bend: 1448.58, 1368.54 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.21 (t, 2H, Methine), 3.09 (d, 2H, Methine), 9.95 (s, 2H,-N-H), 6.30-7.39 (m, 11H, aromatic), 2.37 (s, 3H, CH_3-pyridine).

4. RESULTS AND DISCUSSION

4.1 Chemistry:

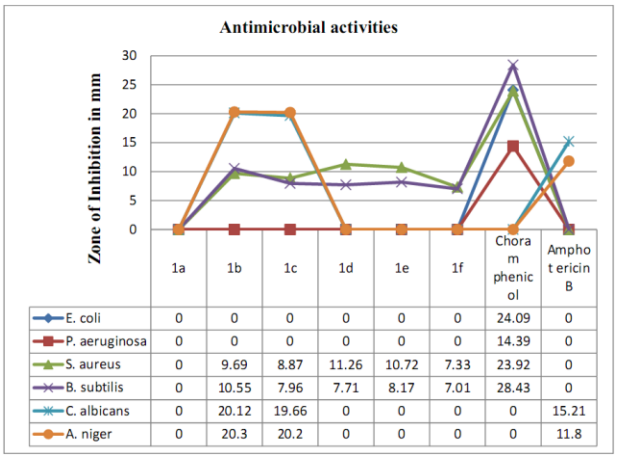
The series of of a novel class of chalcones (1a-c); was comprehended by regimen of N-phenyl succinimides with substituted aromatic aldehyde. Also, a novel class of pyrazoles (1d-f); was comprehended by regimen of chalcones with hydrazine hydrate by solvent free green pathway. The formation of chalcones and pyrazoles derivative was confirmed by IR, 13C NMR and 1H NMR and elemental analysis.

4.2 Antimicrobial Activities:

All the synthesized bis-chalcones 1a-c and bis-pyrazoles 1d-f were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2250) and gram negative bacteria *Escherichia coli* (NCIM 2109), *Pseudomonas aeruginosa* (NCIM 2036) using DMSO solvent. All these novel synthesized compounds were screened against Fungi (Yeast) *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 545). The bacterial cultures were purchased from NCIM: National Collection of Industrial Microorganisms, National Chemical Laboratory (NCL), Pune 411008 [India]. Compound 1a-f showed moderate to good activities against gram positive bacteria *S. aureus* and *B. subtilis*. Also, 1b and 1c exhibited synergetic activities against Fungi *C. albicans* and *A. niger* as shown in the Table –I and Graph –I;

Sr. No.	Sample	*E. coli*	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
		Mean±SD	*Mean ±SD*	*Mean ±SD*	*Mean ±SD*	*Mean ±SD*	*Mean ±SD*
1	1a	- - -	- - -	- - -	- - -	- - -	- - -
2	1b	- - -	- - -	9.69±0.17	10.55±0.11	20.12±0.11	20.30±0.25
3	1c	- - -	- - -	8.87±0.12	7.96±0.13	19.66±0.22	20.20±0.06
4	1d	- - -	- - -	11.26±0.07	7.71±0.15	- - -	- - -
5	1e	- - -	- - -	10.72±0.18	8.17±0.05	- - -	- - -
6	1f	- - -	- - -	7.33±0.11	7.01±0.01	- - -	- - -
	Choram phenicol	**24.09±0.10**	**14.39±0.07**	**23.92±0.17**	**28.43±0.29**	NA	NA
	Amphot ericin B	NA	NA	NA	NA	**15.21±0.15**	**11.8±0.08**

Table-I: Antimicrobial activities of Bis-chalcones 1a-c and Pyrazoles 1d-f



Graph-I: Antimicrobial activities of Bis-chalcones 1a-c and Pyrazoles 1d-f

CONCLUSION

The greener path (microwave assisted) used catalyst Al_2O_3 which is solvent-free and produced sensible yield. 1b and 1c reveals excellent and congenial activities against Fungi *C. albicans* and *A. niger.* Also, the series of compounds 1a-f have showed ameliorate activities against gram positive bacteria *S. aureus* and *B. subtilis*.

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