Biological Evaluation of Some Novel Chalcones and Its Derivatives

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Abstract: CHN analysis Chalcones, (E)-N-(4-(4,6-dichloro-1,3,5-triazin-2-ylamino) phenyl)-3-(4 methoxy-phenyl) acrylamide (4a-c) have been prepared according to Claisen-Schmidt condensation. Further these chalcones (4a-c) on reaction with malononitrile affords cyano-pyridines (5a-c) respectively. The constitutions of newly synthesised compounds have been characterized on the basis of their IR and 1H NMR, 13C NMR spectral data. These synthesized compounds have been screened for their antibacterial and larvicidal activity.

Index Terms: Chalcones, cyanopyridines, Larvicidal activity, antibacterial activity.

I. INTRODUCTION

Heterocyclic compounds are cyclic organic substances which contain at least one atom other than carbon in the ring system. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry. The chemistry of chalcones have generated intensive scientific studies throughout the world, especially interesting are their biological and industrial applications. Chalcone is a generic term given to compounds bearing the 1, 3-diphenyl-2-propen-1-one framework and it belongs to the flavonoid family. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three carbon α, β-unsaturated carbonyl system.

Chalcones are readily synthesized in the laboratory by various synthetic methods. Structural modification of chalcone template can be readily achieved. Chalcones are unsaturated ketones containing the reactive keto and ethylenic group –CO –CH=CH – and are colored compounds because of the presence of the chromophore and auxochromes[1-3]. They are known as benzalacetophenones or benzylideneacetophenones. Kostanecki and Tambor gave the name “Chalcone”[4-5]. These are found to be effective as anti-inflammatory[6,7], anticancer[8-10], antifungal[11-13], cardiovascular[14], and antimalarial[15] agents. The well-known stepwise reaction between cyanuric chloride and aminocetanilide is very well defined, and high yields of aminodichlorotriazines were obtained. Cyanuric chloride is definitely an excellent starting compound for the straightforward preparation of highly structured multitopic molecules. The first substitution is exothermic. Therefore, the temperature of the reaction mixture has to be maintained to 0 ºC. The substitution of the second step at room temperature, finally the third step is functionalized under reflux of the solvent. These observation led us to synthesize some new s-triazinyl based chalcones and it corresponding cyanopyridine derivatives.

II. EXPERIMENTAL MEDTHODOLOGY

Melting points were determined by Deep Vision instrument. The purity of the compounds was checked by TLC using silica gel coated plates and spots were visualized by exposing the dry plates in iodine vapours. IRSpectra were recorded in the solid state, as KBR dispersion by use of the FT-IR-Spectrometer. The 1HNMR and 13C NMR spectra of the compounds were carried out in Bruker AMX 400 MHZ. NMR instrument using CDCl3 or DMSO as a solvent and TMS as internal reference (chemical shift in δ ppm). The mass spectra of the compounds were carried out in ESI Mass.

A. Synthesis of N-(4-(4,6-dichloro-1,3,5-triazin-2-yl amino)phenyl) acetamide (3):

4-amino acetonilide (0.01 mole) was added slowly to cyanuric chloride (0.01 mole) in acetone (30 ml) with constant stirring over a period of 4 hr at 0 to 5º C Then, sodium carbonate (0.05 mole) dissolved in water (10 ml) was added drop wise to neutralize HCl evolved during the reaction. Finally, the contents were poured into crushed ice. The solid was separated out by filtration and washed with water. The product is dried, recrystallized from alcohol to give the product (3).
B. Synthesis of (E)-N-(4-(4,6-dichloro-1,3,5- triazin-2-ylamino) phenyl)-3-(4-methoxyphenyl) acrylamide (4a):

Acetamide compound (3) (0.01 mole) was dissolved in ethanol (30 ml) Then 10% NaOH solution and 4-Methoxybenzaldehyde (0.01 mole) was added to the reaction mixture with constant stirring over a period of 6 hrs. The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product (4a) is dried, recrystallized from ethanol. IR (KBR) cm⁻¹ : C=N,s-triazine (829.90), CN-H str (3149.04), C=Cl (770.81).

C. Synthesis of (E)-N-(4-(4,6-dichloro-1,3,5- triazin-2-ylamino) phenyl)-3-(4-fluorophenyl) acrylamide (4b):

Acetamide compound (3) (0.01 mole) was dissolved in ethanol (30 ml) Then 10% NaOH solution and 4-Flurobenzaldehyde (0.01 mole) was added to the reaction mixture with constant stirring over a period of 6 hrs. The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product (4b) is dried, recrystallized from ethanol. IR (KBR) cm⁻¹ : C=N,s-triazine (850.95), N-H str (2926.45), C=Cl (764.63).

D. Synthesis of (E)-N-(3-(4,6-dichloro-1,3,5- triazin-2-ylamino) phenyl)-3-(benzo [d] [1,3] dioxol-5-yl) acrylamide (4c):

Acetamide compound (3) (0.01 mole) was dissolved in ethanol (30 ml) Then 10% NaOH solution and Piperonal (0.01 mole) was added to the reaction mixture with constant stirring over a period of 6 hrs. The reaction mixture was poured into crushed ice. The solid was separated out by filtration and washed with water. The product is dried, recrystallized from ethanol. IR (KBR) cm⁻¹ : C=C (1508.06), C=N (1613.16), C=Cl (1119.40), N-H str (1209.92), C=Cl (770.81).

E. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2-ylamino)phenyliamino)-2-amino-4-(4-methoxyphenyl) pyridine-3-carbonitrile (5a):

A mixture of a compound (4a) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole), ammonium acetate (0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured into crushed ice. The product (5a) separated out was filtered washed and recrystallized from alcohol. IR(KBR) cm⁻¹ : C=Cl (813.61), Ar C-Cl (834.80), Ar-C (1200.45), N-H str (3419.04), C=Cl (770.81), S str (2922.59), C─Cl (764.63).

F. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2-ylamino)phenyliamino)-2-amino-4-(4-fluorophenyl) pyridine-3-carbonitrile (5b):

A mixture of a compound (4b) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole), ammonium acetate (0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured into crushed ice. The product (5b) separated out was filtered washed and recrystallized from alcohol. IR(KBR) cm⁻¹ : C=Cl (776.208), Ar C-Cl (1129.12), Ar-N str (1380.78), primary N-H (1509.07), C=C (1626.66), N-H str (2918.73), 1H NMR(CDCl₃) δ ppm : 4.296 to 4.314 (S,1H,s-triazine Ar-C-NH), 4.311 to 4.331 (S,1H,Ar-C-NH), 6.986-7.437 (d, 4H, Ar-CH), 7.588 (Ar-H), 9.898 (2-Py-Ar-CH). 13C NMR(CDCl₃) δ ppm: Ar-CH (119.40 to 121.02), 2-Py-CH (134.15 to 135.28), S-triazine (168.20).

G. Synthesis of 5-(4-(4,6-dichloro-1,3,5 triazin-2-ylamino)phenylamino)-2-amino-4-(benzo [d] [1,3] dioxol 4-yl pyridine-3-carbonitrile (5c):

A mixture of a compound (4c) (0.01 mole) dissolved in 40 ml ethanol and added malononitrile (0.01 mole), ammonium acetate (0.08 mole) was refluxed for 8 hrs. Then the mixture was cooled and poured into crushed ice. The product (5c) separated out was filtered washed and recrystallized from alcohol. C=C (1578.45), IR(KBR) cm⁻¹ : C=Cl (813.61), O=C-C (1032.69), Ar C-Cl (1108.87), Ar-N (1334.50), primary N-H (1508.06), C=N (1616.06), N-H str (2922.59), O-H str (3784.62), 1H NMR(CDCl₃) δ ppm : 4.427(S,1H,s-triazine Ar-C-NH), 5.276(S,1H,Ar-C-NH), 6.672 (d,1H,Ar-Py), 6.983-7.469 (d, 4H, Ar-CH). 13C NMR(CDCl₃) δ ppm: Ar-CH (108.82 to 121.53), 2-Py-CH (134.65 to 148.38), 1-imine (166.01), S-triazine (166.24).

III. RESULT AND DISCUSSION

The interest of organic chemistry in 2,4,6-trichloro-1,3,5-triazine as a starting material is due to temperature dependent reactivity of one chlorine atom that allow a sequential introduction of various substituents. In the present article we have reported the synthesis, characterization and antibacterial and Larvicidal activity of some novel s-triazine based cyanopyridine derivatives.

A. Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method against S. aureus and E. faecalis (Gram positive bacteria) and E.coli, S.Typi (Gram negative bacteria) by using agar medium.Ciprofloxacin was used as standard drugs for the comparison of antibacterial activity by visualizing activity data it could be observed that compounds (5a-c) were found to be active or inactive against all bacterial strain. (Table No. 2)

B. Larvicidal Activity

For the bioassay test, larvae were taken in five batches of 20 in 249 ml of water and 1.0 ml of the desired chemical extract concentration. The numbers of dead larvae were counted after 24 h of exposure and the percentage of mortality was reported from the average of five replicates.
C. Spectral Data

4a-^1^H NMR

Current Data Parameters
NAME            MK-EX-6
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20170304
Time              10.22
INSTRUM           spect
PROBHD   5 mm DUL 13C-1
POLAROOG          zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8223.685 Hz
FIDRES         0.125483 Hz
AQ            3.9846387 sec
RG                  228
DW               60.800 usec
DE                 6.00 usec
TE                296.2 K
D1           1.00000000 sec
td0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                11.42 usec
P21               -3.00 dB
SPOL            400.1324710 MHz

F2 - Processing parameters
SI                32768
SF            400.1300051 MHz
WDM          EM
SSB            0.35 Hz
GB              0
PC                1.00
Current Data Parameters
NAME        MK-II-TT-27
EXPNO                 2
PROCNO                2

F2 - Acquisition Parameters
Date_          20180703
Time               9.29
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PROBHD   5 mm BBO BB-1H
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                  512
DS                    4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ            1.3631988 sec
RG                  406
DW               20.800 usec
DE                 6.00 usec
TE                296.3 K
D1          2.00000000 sec
g11          0.03000000 sec
delta         1.89999999 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
Pl                 14.35 usec
Pl1               -1.00 dB
SP01        400.1324710 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
Nuc2                     1H
PCPD2                 90.00 usec
Pl12              14.17 dB
Pl13              120.00 dB
Pl22             -1.00 dB
SP02        400.1316005 MHz

F2 - Processing parameters
SI                32768
SF          100.6127950 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
Table 1: Physical data of the synthesized compounds (4a-c) and (5a-c)

<table>
<thead>
<tr>
<th>Compound code</th>
<th>R</th>
<th>Mol. Formula</th>
<th>Mol. weight</th>
<th>MP(ºC)</th>
<th>Yield(%)</th>
<th>Rf value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₆H₄OCH₃</td>
<td>C₁₉H₁₅Cl₂N₅O₂</td>
<td>416.26</td>
<td>190-191 ºC</td>
<td>89%</td>
<td>0.61</td>
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<tr>
<td>4b</td>
<td>C₆H₄F</td>
<td>C₁₇H₁₃Cl₂FN₅O</td>
<td>404.23</td>
<td>194-196 ºC</td>
<td>75%</td>
<td>0.70</td>
</tr>
<tr>
<td>4c</td>
<td>C₇H₃O₂</td>
<td>C₁₉H₁₃Cl₂N₅O₃</td>
<td>430.24</td>
<td>206-208º C</td>
<td>83%</td>
<td>0.53</td>
</tr>
<tr>
<td>5a</td>
<td>C₆H₄OCH₃</td>
<td>C₂₂H₁₄Cl₂N₅O₂</td>
<td>479.32</td>
<td>115-120 ºC</td>
<td>70 %</td>
<td>0.55</td>
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<tr>
<td>5b</td>
<td>C₆H₄F</td>
<td>C₁₇H₁₃Cl₂FN₈</td>
<td>467.29</td>
<td>138-140º C</td>
<td>75%</td>
<td>0.65</td>
</tr>
<tr>
<td>5c</td>
<td>C₇H₅O₂</td>
<td>C₂₂H₁₄Cl₂N₅O₂</td>
<td>493.30</td>
<td>123-125º C</td>
<td>62 %</td>
<td>0.61</td>
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Table 2: Elemental analysis of the synthesized compounds (4a-c) and (5a-c)

<table>
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<th>Compound code</th>
<th>Mol. Formula</th>
<th>Appearance</th>
<th>Elemental Analysis</th>
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</thead>
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<td></td>
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<td>% C Calcd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(found)</td>
</tr>
<tr>
<td>4a</td>
<td>C₁₉H₁₅Cl₂N₅O₂</td>
<td>Light yellow</td>
<td>54.82</td>
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<td></td>
<td></td>
<td>(54.80)</td>
</tr>
<tr>
<td>4b</td>
<td>C₁₈H₁₂Cl₂N₅OF</td>
<td>Half white</td>
<td>53.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(53.46)</td>
</tr>
<tr>
<td>4c</td>
<td>C₁₉H₁₃Cl₂N₅O₃</td>
<td>Pale yellow</td>
<td>53.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(53.03)</td>
</tr>
<tr>
<td>5a</td>
<td>C₂₂H₁₆Cl₂N₅O</td>
<td>Greenish yellow</td>
<td>55.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(55.10)</td>
</tr>
<tr>
<td>5b</td>
<td>C₂₁H₁₃Cl₂FN₈</td>
<td>Dark brown</td>
<td>53.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(53.95)</td>
</tr>
<tr>
<td>5c</td>
<td>C₂₂H₁₄Cl₂N₅O₂</td>
<td>Brown</td>
<td>53.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(53.66)</td>
</tr>
</tbody>
</table>

Table 3: Larvicidal activity

<table>
<thead>
<tr>
<th>S.No</th>
<th>Chemical name with concentration</th>
<th>Effectiveness after 24 Hrs in % of killing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>72%</td>
</tr>
</tbody>
</table>
Figure 1. In vitro antibacterial activity data of s-triazine derivatives against tested organisms.

Standard = Ciprofloxacin
A1- Compound 5a  B1- Compound 5b,  C1- Compound 5C,
CONCLUSION

We have successfully synthesized a new series of chalcone derivatives and moreover, some compounds contain bioactive heterocyclic moiety. The antibacterial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested organism. The compounds showed good larvicidal activity.

ACKNOWLEDGEMENT

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REFERENCES