Research Journal of Agricultural Sciences
An International Journal

Res. Jr. of Agril. Sci. **12**(1): 278–280

P- ISSN: 0976-1675 | **E**- ISSN: 2249-4538

www.rjas.org

Short Communication

Synthesis of 6-Amino-1-aryloxyaceto-4-aryl-5-cyano-3-methyl-1, 4, 5, 7-tetrahydro pyrazolo[4,5-e]pyridines Derivatives as Potential Molluscicidal Agent

Akhilesh Singh[1], Abhishek Singh*[2] and P. Singh[3]

Received: 22 Oct 2020 | Revised accepted: 23 Jan 2021 | Published online 08 Feb 2021

***Key words*:** Pyridines, Pyrazolo, Molluscicidal activity, *Lymnaea acuminate*

Pyrazoles are known to exhibit broad spectrum of acivities. The pyridine ring is associated with diverse biological activities probably by virtue of incorporating polar groups –CN, C=O, -NH and $–CH_2$ the importance of which has been well stressed in many pesticidal properties [1]. In continuation of our work on fused heterocycles of pesticidal interest and guided by observation that the fusion of two or more heterocyclic nuclei often enhances the biological profile many folds than its parent nuclei; we have undertaken the synthesis and bioassay of titled compounds [2]. The investigation further appeared interesting because compactness and planarity of such a ring system may be an additional factor for enhancing biological profile.

The required synthon 1-aryloxyaceto-3-methylpyrazol-5-one (I) were prepared according to the literature method. The synthon (I) fused with 4-substituted bezaldehyde in presence of sodium acetate and acetic acid yilded 1-aryloxyaceto-4-arylidine-3-methyl-pyrazol-5-one (II) which on treatment with malenonitrile and ammonium acetate in dioxane gave the desire compounds (III).

Procedure for one typical case for each step has been described. All melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-157 spectrophotometer (cm^{-1}), ^1H NMR spectra in DMSO-d_6 on a Varian EM-360 (200 MHz) spectrometer using TMS as internal reference (chemical shift in δ ppm).

1-(4-Methylphenoxylaceto)-4-(4-hydroxyphenylidene)-3-mthyl-pyrazol-5-one (IIk)

Requisite, 1-(4-Methylphenoxylaceto)-3-mthyl-pyrazol-5-one (2.46g, .01M), 4-hydroxybenzaldehyde (1.22g, .01M) and fused sodium acetate (1.64g, 0.02M) was refluxed in glacial acetic acid for three hours. The reaction mixture was cooled, poured into water. The precipitated mass was filtered, washed with water, dried and recrystallized from aq. ethanol. m. p. 175^0C, yield (67%). IR (KBr): 3490(-OH), 1705(C=O), 1660 (-COC=CH-), 1630(C=N), 1530 (aromatic ring); ^1H NMR (DMSO-d_6): δ2.05(s, 3H, $-CH_3$), 2.25(s, 3H, $-CH_3$), 2.81(s, 1H, CH), 4.58(s, 2H, $-OCH_2$), 6.52-7.55(m, 8H, Ar-H), 9.3(s, 1H, -OH).

The spectral data of few more such compounds are as under:

IIa: IR (KBr):1705(C=O), 1665 (-COC=CH-), 1635(C=N), 1205(C-O) 1537 (aromatic ring); ^1H NMR (DMSO-d_6): δ2.07(s, 3H, $-CH_3$), 2.25(s, 3H, $-CH_3$), 2.81(s, 1H, CH), 4.55(s, 2H, $-OCH_2$), 7.03-8.00(m, 8H, Ar-H), 3.8(s, 3H, $-OCH_3$).

IIg: IR (KBr): 3490 (-OH), 1705(C=O), 1665 (-COC=CH-), 1635(C=N), 1205(C-O) 1537 (aromatic ring); ^1H NMR (DMSO-d_6): 2.25(s, 3H, $-CH_3$), 2.81(s, 1H, CH), 4.55(s, 2H, $-OCH_2$), 7.03-7.58(m, 8H, Ar-H), 9.5(s, 1H, -OH). Other compounds of the type **II** were prepared similarly and are recorded in (Table 1).

2-Amino-1-(4-Methylphenoxylaceto)-4-(4-hydroxypheny)-5-cyano-3methyl-1, 4, 5, 7-tetrahydropyrazolo [4, 5-e] pyridine(IIIk) Requisite 1-(4-Methylphenoxylaceto)-4-(4-hydroxyphenylidene)-3-mthyl-pyrazol-5-one (4.05g, 0.01M), malenonitrile (dicanomethane) (0.72g, 0.01M) and ammonium acetate (6.16g, 0.08M) was refluxed in dioxane for six hours. The reaction mixture was cooled, poured into water. The precipitated mass was filtered, washed with water, dried and recrystallised from aq. ethanol. m. p. 222^0C, yield (65%). IR (KBr): 3400(-OH), 3240(N-H), 2160 ($-C\equiv N$), 1740(C=O), 1630(C=N), 1500(aromatic ring); ^1H NMR (DMSO-d_6): δ2.07(s, 3H, $-CH_3$), 2.27(s, 3H, $-CH_3$), 4.58(s, 2H, $-OCH_2$), 8.1(s, 1H, -NH), 6.88-7.70(m, 8H, Ar-H), 9.3(s, 1H, -OH).

IIIa: IR (KBr): 3240(N-H), 2163($-C\equiv N$), 1740(C=O),1630(C=N), 1500(aromatic ring);1210(C-O); ^1H NMR (DMSO-d_6): 2.24(s, 3H, $-CH_3$), 4.60(s, 2H, $-OCH_2$), 7.9(s, 1H, -NH), 7.53-7.79(m, 9H, Ar-H), 4.0(s, 3H, $-OCH_3$).

IIIg: IR (KBr): 3405(-OH), 3235(N-H), 2166($-C\equiv N$), 1745(C=O),1630(C=N), 1505(aromatic ring);1212(C-O); ^1H NMR (DMSO-d_6): 2.22(s, 3H, $-CH_3$), 4.59(s, 2H, $-OCH_2$), 8.3(s, 1H, -NH), 7.50-7.75(m, 9H, Ar-H), 9.6(s, 1H, -OH).

Other compounds of the type **III** were prepared similarly and are recorded in (Table 1). All compounds gave satisfactory elemental analysis.

***Abhishek Singh**
abhupc@gmail.com

[1-3]Department of Chemistry, K. S. Saket P.G. College, Ayodhya - 224 001, Uttar Pradesh, India

[2]Department of Chemistry, U. P. Autonomous College, Varanasi - 221 002, Uttar Pradesh, India

Table 1 Physical data of the compounds prepared

S. No.	R	R'	M.P (°C)	Yield (%)	Mol. Formula	Analysis found (Calc%) of		
						C	H	N
IIa.	H	2-OCH_3	120	50	$C_{20}H_{18}N_2O_4$	68.43 (68.57)	5.27 (5.14)	8.09 (8.00)
IIb.	2-Cl	4-OCH_3	124	52	$C_{20}H_{17}N_2O_4Cl$	62.54 (62.42)	4.30 (4.42)	7.37 (7.28)
IIc.	4-Cl	4-OCH_3	103	49	$C_{20}H_{17}N_2O_4Cl$	62.53 (62.42)	4.31 (4.42)	7.38 (7.28)
IId.	2,4-Cl_2	4-OCH_3	135	70	$C_{20}H_{16}N_2O_4Cl_2$	57.32 (58.28)	3.90 (3.82)	6.53 (6.68)
IIe.	2-CH_3	4-OCH_3	113	55	$C_{21}H_{20}N_2O_4$	69.34 (69.23)	5.42 (5.43)	7.71 (7.69)
IIf.	4-CH_3	4-OCH_3	95	82	$C_{21}H_{20}N_2O_4$	69.33 (69.23)	5.43 (5.49)	7.72 (7.69)
IIg.	H	4-OH	159	51	$C_{19}H_{16}N_2O_4$	67.89 (67.86)	4.85 (4.76)	8.21 (8.33)
IIh.	2-Cl	4-OH	170	59	$C_{19}H_{15}N_2O_4Cl$	61.62 (61.54)	4.01 (4.05)	7.65 (7.57)
IIi.	4-Cl	4-OH	165	49	$C_{19}H_{15}N_2O_4Cl$	61.62 (61.54)	4.01 (4.05)	7.65 (7.57)
IIj.	2,4-Cl_2	4-OH	170	51	$C_{19}H_{14}N_2O_4Cl_2$	56.43 (56.30)	3.54 (3.46)	6.83 (6.91)
IIk.	4-CH_3	4-OH	175	67	$C_{20}H_{18}N_2O_4$	68.43 (68.57)	5.25 (5.14)	8.20 (8.00)
IIIa.	H	2-OCH_3	171	40	$C_{23}H_{21}N_5O_3$	66.34 (66.51)	5.26 (5.06)	16.61 (16.86)
IIIb.	2-Cl	4-OCH_3	175	67	$C_{23}H_{20}N_5O_3Cl$	61.25 (61.40)	4.25 (4.45)	15.53 (15.57)
IIIc.	4-Cl	4-OCH_3	155	56	$C_{23}H_{20}N_5O_3Cl_2$	61.20 (61.40)	4.35 (4.45)	15.57 (15.53)
IIId.	2,4-Cl_2	4-OCH_3	140	55	$C_{23}H_{19}N_5O_3Cl_2$	56.83 (57.02)	4.04 (3.93)	14.56 (14.46)
IIIe.	2-CH_3	4-OCH_3	170	47	$C_{24}H_{23}N_5O_3$	67.03 (67.13)	5.20 (5.36)	16.43 (16.31)
IIIf.	4-CH_3	4-OCH_3	160	87	$C_{24}H_{23}N_5O_3$	67.00 (67.13)	5.16 (5.36)	16.43 (16.31)
IIIg.	H	4-OH	190	58	$C_{22}H_{19}N_5O_3$	65.73 (65.83)	4.95 (4.74)	17.44 (17.46)
IIIh.	2-Cl	4-OH	240	88	$C_{22}H_{18}N_5O_3Cl$	60.67 (60.61)	4.18 (4.13)	16.25 (16.07)
IIIi.	4-Cl	4-OH	120	85	$C_{22}H_{18}N_5O_3Cl$	60.97 (60.61)	4.28 (4.13)	16.25 (16.07)
IIIj.	2-CH_3	4-OH	160	81	$C_{23}H_{21}N_5O_3$	66.32 (66.51)	5.23 (5.06)	16.60 (16.87)
IIIk.	4-CH_3	4-OH	221	65	$C_{23}H_{21}N_5O_3$	66.33 (66.51)	5.03 (5.06)	17.03 (16.87)

Biological activity

The molluscicidal activity of the compounds was evaluated against the snail *Lymnaea acuminata* which is a vector of the giant liver flukes *Fasciola gigantica* and *Fasciola hepatica*. It causes endemic fasciolosis in cattle population of eastern Uttar Pradesh.

Being herbivorous, these snails cause damage to submerged paddy crops especially in Terai region of U.P. In this region the water reservoirs and submerged paddy fields have become foci for such snail pests.

Adult *L. acuminata* were collected from ponds, lakes and low-lying submerged fields and were used as test animals. The snails were acclimatized for 72 hr in laboratory condition. Six sets of glass aquarium were used for each concentration of experiment. Ten adult snails were kept in each glass aquaria containing 3l dechlorinated tap water. Toxicity of different compounds was determined by the method of [3]. The snails were treated with different concentrations of compounds. Mortality was recorded at 24 hr intervals up to 96 hr exposure periods. Control animals were kept in a similar manner without treatment. Dead snails were removed from the aquarium to avoid contamination of water. No response to the needle probe confirmed the death of the snail.

For one compound **IIa** (arbitrarily chosen) lethal concentration (LC_{50}) values, lower and upper confidence limits (LCL and UCL), g-values, t-ratio values, slope values and heterogeneity values were calculated according to the method of POLO computer program of [4] (Table 2).

Table 2 Toxicity of compound IIa against *L. acuminata*#

Period (hrs)	LC^*_{50}(LCL-UCL) mg/l	Slope	t-ratio	Heterogeneity	g
24	2.05(1.60-4.04)	3.33±0.85	3.92	0.38	0.25
48	1.78(1.42-3.49)	2.74±0.74	3.66	0.20	0.28
72	9.01(0.90-1.16)	3.27±0.71	4.58	0.20	0.18
96	0.76(0.66-0.84)	4.64±0.82	5.60	0.28	0.12

#Six batches of 10 snails were exposed to different concentrations of the treatment. Mortality was determined every 24 hr. Concentrations given are the final concentration in the aquarium water.

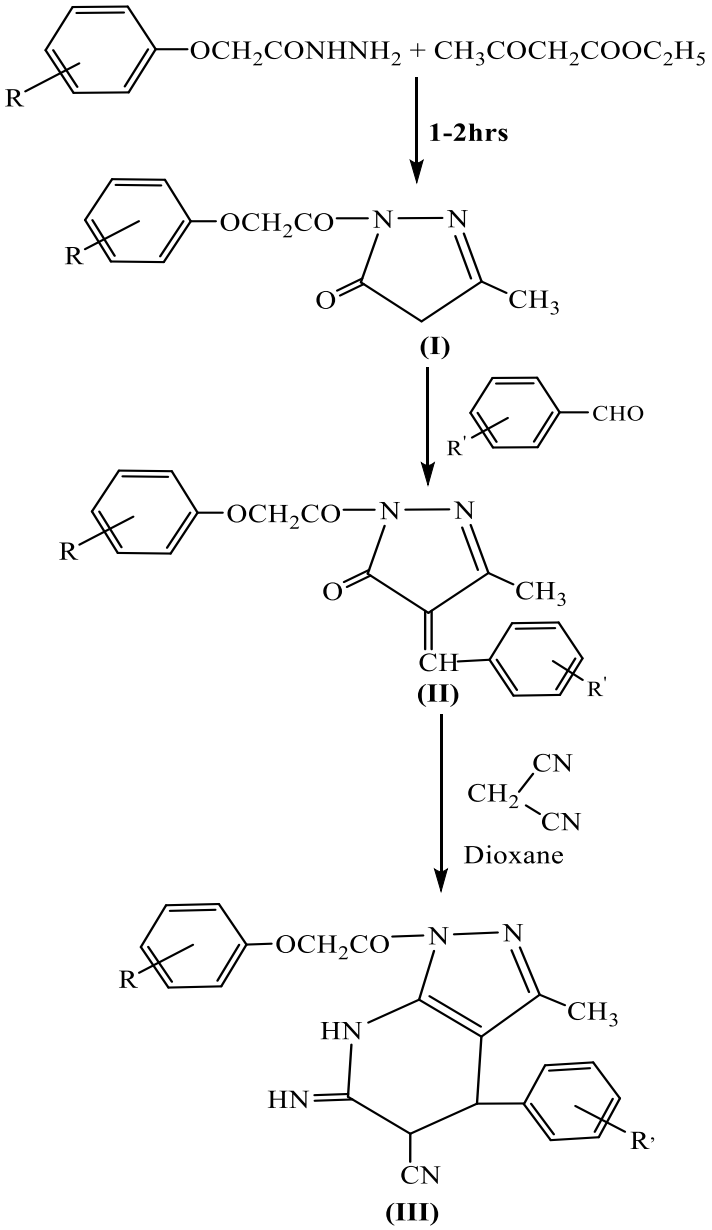
*The LC_{50} values of remaining compounds can be obtained from the authors on request.

The molluscicidal data indicates that all tested compounds showed strong to moderate activities. The molluscicidal activity of the tested compounds is dose and time dependent. Nature of substituents is critical to molluscicidal activity. The electron donating substituents such as methyl, methoxy enhanced the molluscicidal activity. On the other hand, the electron withdrawing groups such as chloro decreased the molluscicidal activity [5]. The slope values were steep and separate estimation of LC_{50} based on each of the six replicates was found to be within the 95% confidence limits of LC_{50}. The steep slope values indicated that even small increase in the concentration causes mortality in the snails. The 't' ratio is greater than 1.96, which indicates that regression is significant. Values of heterogeneity factor less than 1 denote that in the replicate of random sample the concentration response line would fall within 95%, confidence limit and thus the model fits the data adequately [6]. The index of significance of potency estimation g-value indicates that the value of the mean is within limits at all probability (90, 95, and 99) as it is less than 0.5.

SUMMARY

Several 6-Amino-1-aryloxyaceto-4-aryl-5-cyano-3-methyl-1,4,5,7-tetrahydro pyrazolo[4,5-e]pyridines **(III)** have been synthesized from synthon 1-aryloxyaceto-4arylidine-3-methyl-pyrazol-5-ones **(II).** The molluscicidal activity of few titled compounds has been evaluated against the snail

Lymnaea acuminate. The LC_{50} slope, t-ratio heterogeneity and g-values have been determined and discussed.



Scheme 1

Acknowledgement

The authors are thankful to RSIC (CDRI), Lucknow for recording spectra and carrying out elemental analysis. Authors are also thankful to Dr. D. K. Singh, Professor (Rtd), Department of Zoology, DDU Gorakhpur University Gorakhpur for help in evaluating molluscicidal activities.

LITERATURE CITED

1. Shunan K, Melboureen S, Singha LI, Vishwakarma JN. 2020. Ultrasound assisted synthesis of pyrazolo[1,5-a]pyrimidine-antipyrine hybrids and their anti-inflammatory and anti-cancer activities. *European Journal of Chemistry* 11(1): 68-79.
2. Ibrahim YR. 2009. Synthesis of spiro(cyclohexa-diene-pyrazolo[1,5-a]pyrimidine-4-ylidene)-malononitrile derivatives. *Journal of Chemical Research* 8: 495-498.
3. Rao IG, Singh DK. 2001. Combinations of *Azadirachta indica* and *Cedrus deodara* oil with piperonyl butoxide, MGK-264 and *Embelia ribes* against *Lymnaea acuminata*. Chemosphere 44(8): 1691-1695.
4. Russell RM, Robertson JL, Savin NE. 1977. POLO: A new computer program for probit analysis. *Bull. Entomol. Soc. Am*. 23: 209-213.
5. Sindhu J, Singh H, Khurana JM, Bhardwaj JK, Saraf P, Sharma C. 2016. Synthesis and biological evaluation of some functionalized 1H-1,2,3-triazole tethered pyrazolo[3,4-b]pyridin-6(7H)-ones as antimicrobial and apoptosis inducing agents. *Medicinal Chemistry Research* 25(9): 1813-1830.
6. Shunan K, Ivee B, Singha LI, Philippe H, Vishwakarma JN. 2015. A facile, regioselective synthesis of novel 3-(N-phenylcarboxamide)pyrazolo[1,5-a]pyrimidine analogs in the presence of KHSO $$_{4}$$ 4 in aqueous media assisted by ultrasound and their antibacterial activities. *Molecular Diversity* 20(2): 379-390.