

Synthesis, characterization and physiological activity of some novel isoxazoles

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Abstract. Hushare VJ, Rajput PR, Malpani MO, Ghodile NG. 2012. Synthesis, characterization and physiological activity of some novel isoxazoles. *Nusantara Bioscience* 4: 81-85. A series of chlorosubstituted 4-arylisoxazoles have been synthesized by refluxing chlorosubstituted-3-aryylflavones and 3-alkoylchromone with hydroxylamine hydrochloride in dioxane medium containing 0.5 mL piperidine. Chlorosubstituted-3-aryylflavones and chlorosubstituted-3-alkoylchromone were prepared by refluxing them separately with iodine crystal in ethanol. Initially chlorosubstituted-3-aryylflavanones and 3-alkoylchromanone were prepared by the interaction of different aromatic and aliphatic aldehydes with 1-(2'-hydroxy-3',5'-dichlorophenyl)-3-phenyl-1,3-propanedione. Constitutions of synthesized compounds were confirmed on the basis of elemental analysis, molecular weight determination, UV-Visible, I.R., and ¹H-NMR spectral data. The titled compounds were evaluated for their growth promoting activity on some flowering plants viz. *Papaver rhoeas*, *Calendula officinalis*, *Gladiola tristis*, *Gaillardia aristata*, *Dianthus chinensis*, and *Iberis* sp. (candytuft). The results indicate that applicated plants had higher shoots and more number of leaves.

Keywords: chlorosubstituted 3-aryylflavanones, 3-alkoylchromanone, 3-aryylflavones, 3-alkoylchromone, isoxazoles.

Abstrak. Hushare VJ, Rajput PR, Malpani MO, Ghodile NG. 2012. Sintesis, karakterisasi dan aktivitas fisiologis beberapa isoxazoles baru. *Nusantara Bioscience* 4: 81-85. Serangkaian chlorosubstituted-4-arylisoxazoles telah disintesis dengan mencampur chlorosubstituted-3-aryylflavones dan 3-alkoylchromone dengan hidroksilamin hidroklorida dalam medium dioksan yang mengandung 0.5 mL piperidine. Chlorosubstituted-3-aryylflavones dan chlorosubstituted-3-alkoylchromone dibuat dengan cara mencampur keduanya secara terpisah dengan yodium kristal dalam etanol. Awalnya, chlorosubstituted-3-aryylflavanones dan 3-alkoylchromanone dibuat melalui interaksi antara aldehida aromatik dan alifatik yang berbeda dengan 1-(2'-hidroksi-3',5'-Diklorofenil)-3-fenil-1,3-propanedione. Senyawa yang terbentuk diuji berdasarkan analisis unsur, berat molekul, serta data spektrum UV-Vis, IR dan ¹H-NMR. Senyawa tersebut dievaluasi aktivitas fisiologisnya dalam mendorong pertumbuhan beberapa tanaman berbunga, yaitu: *Papaver rhoeas*, *Calendula officinalis*, *Gladiola tristis*, *Gaillardia aristata*, *Dianthus chinensis*, dan *Iberis* sp. (candytuft). Hasilnya, tanaman yang diaplikasi dengan senyawa tersebut lebih tinggi dan jumlah daunnya lebih banyak.

Kata kunci: chlorosubstituted 3-aryylflavanones, 3-alkoylchromanone, 3-aryylflavones, 3-alkoylchromone, isoxazoles.

INTRODUCTION

Heterocyclic compounds are widely distributed in nature and are essential for the sustainable of life on earth (Joule and George 1978). The azoles containing one oxygen and one nitrogen atom at 1, 2-position are designated as isoxazoles. Isoxazole derivatives have been found to possess a broad spectrum of biological activities such as anti-inflammatory (Balvi and Anzaldi et. al. 2005), antibacterial (Magar et al. 2011), anticonvulsant (Muthukumar et al. 2011), antibiotic (Doyle et al. 1961), anti-tubercular (Haripara et al. 2004) anxiolytic (Wagner et al. 2004), antiepileptic (Schwate and Willmre 2001), PPAR- δ (Epple et al. 2006), agonists, acetylcholine-esterase (Mantelingu et al. 2004) and erosive inhibitor (Gupta et al. 2005), antifungal (Flores et al. 2006), anti-tumor (Ramana and Reddy 2011), analgesic (Osman et al.

2012), chemotherapy (Hamada and Sharshira 2011), antiarthritic (Patterson et al. 1992), antiviral (Goda et al. 2003), anesthetic, anticancer, hypolipidemic (Coutouli-Argyropoulou et al. 2006), antiarrhythmic (Inoue et al. 1991), insect antifeedant (Soni et al. 2006), glycogen phosphorylaseinhibitor (Benlifa et al. 2006), antipsychotic (Markourtz et al. 1999), anticoagulant (Qan et al. 1999), acetylcholine esterase inhibitor (Mantelingu et al. 2004), CNS active (Griesbeck et al. 2011), isoxazole derivatives controlled *Botrytis cinerea* on cucumbers (Shionogi and Co. Ltd. 1983) and thrombosis (Padmavathi et al. 2000). One of the isoxazole derivatives was found to have antiviral properties against herpes type-2 virus (Sterling Drug Inc 1982), whereas some isoxazole derivatives also reported having corrosion inhibitor properties for fuels and lubricants (Marzinik and Felder 1997).

The newly synthesized compounds successfully screened for their growth promoting impact on some flowering plants, viz. *Papaver rhoeas*, *Calendula officinalis*, *Gladiola tristis*, *Gaillardia aristata*, *Dianthus chinensis*, and *Iberis* sp.

MATERIALS AND METHODS

This research includes synthesis, characterization and physiological activity test of some novel isoxazoles on some flowering plants. The melting points of all synthesized compounds were recorded using hot paraffin bath and are uncorrected. Chemicals used were of A.R. Grade. ^1H NMR spectra using acetone. I.R. spectra were recorded on Perkin-Elmer spectrophotometer in the range $4000\text{--}400\text{ cm}^{-1}$ in nujol mull and as KBr pellets. UV-VIS spectrums were recorded in nujol medium.

RESULTS AND DISCUSSION

Synthesis of new isoxazoles

Synthesis pathway of novel compounds of isoxazoles is shown in Figure 1.

Synthesis of 2-benzoyloxy-3, 5-dichloroacetophenone (3a). 2-Hydroxy-3, 5-dichloroacetophenone (2a) (0.04 mol) and benzoyl chlorides (0.05 mol) were dissolved in 10% NaOH (30 mL). The reaction mixture was shaken for about half an hour. The products thus separated was filtered washed with water followed by sodium bicarbonate (10%) washing and then again with water. The solid product thus separated was crystallized from ethanol to get the compound m.p. 64°C .

Synthesis of 1-(2'-hydroxy-3', 5'-dichlorophenyl)-3-phenyl-1, 3-propanedione (4a). 2-Benzoyloxy-3, 5-dichloroacetophenone (3a) (0.05 mol) was dissolved in dry pyridine (40 mL). The solution was warmed up to 60°C and pulverized KOH (15 g) was added to it slowly with constant stirring. Then it was kept overnight and acidified by adding ice cold HCl (10%). The brownish yellow solid product thus separated was filtered, washed with sodium bicarbonate solution (10%) and finally again with water. It was then crystallized from ethanol to get the compound (4a) m.p. 110°C .

Synthesis of 3-benzoyl-2-(4'-nitrophenyl)-6, 8-dichloroflavanone (5a). A mixture of 1-(2'-hydroxy-3', 5'-dichlorophenyl)-3-phenyl-1,3-propanedione (4a) (0.01 mol) and p-nitrobenzaldehyde (0.02 mol) was refluxed in dioxane (25 mL) containing 0.5 mL piperidine for 15 -20 min. After cooling the reaction mixture was acidified with dil. HCl (20%). The product thus separated was crystallized from ethanol to get the compound (5a). Similarly 3-benzoyl-2-(4'-chlorophenyl)-6,8-dichloro-flavanone (5b) and 3-benzoyl-2-butyl-6,8-dichlorochromone (5c) were synthesized separately from the compound (4a) by using p-chlorobenzaldehyde and valeraldehyde respectively.

Synthesis of 3-benzoyl-2-(4'-nitrophenyl)-6, 8-dichloroflavanone (6a). 3-Benzoyl-2-(4'-nitrophenyl)-6, 8-dichloroflavanone (5a) (0.01 mol) was refluxed for about

10 minutes with crystal of iodine in ethanol (20 mL). After cooling the reaction mixture was diluted with water. The solid product thus separated was filtered, washed with sodium bicarbonate solution and then with water. Finally, it was crystallized from ethanol to get the compound (6a). Similarly compounds 3-benzoyl-2-(4'-chlorophenyl)-6, 8-dichloroflavone (6b) and 3-benzoyl-2-butyl-6, 8-dichlorochromone (6c) were synthesized separately from the compounds (5b) and (5c) respectively.

Synthesis of 3-(2'-hydroxy-3', 5'-dichlorophenyl)-4-benzoyl-5-(4''-nitrophenyl)-isoxazole (7a). A mixture of 3-benzoyl-2-(4'-nitrophenyl)-6,8-dichloroflavone (6a) (0.01 mol) and hydroxylamine hydrochloride (0.02 mol) was refluxed in dioxane (20 mL) containing 0.5 mL piperidine for two hours. After cooling the reaction mixture was diluted with water. The product thus separated was filtered crystallized from ethanol to get the compound (7a). Similarly other compounds 3-(2'-hydroxy-3', 5'-dichlorophenyl)-4-benzoyl-5-(4''-chlorophenyl)-isoxazole (7b) and 3-(2'-hydroxy-3', 5'-dichlorophenyl)-4-benzoyl-5-butyl-isoxazole (7c) were synthesized separately from the compounds (6b) and (6c) respectively.

Characterization of titled compounds

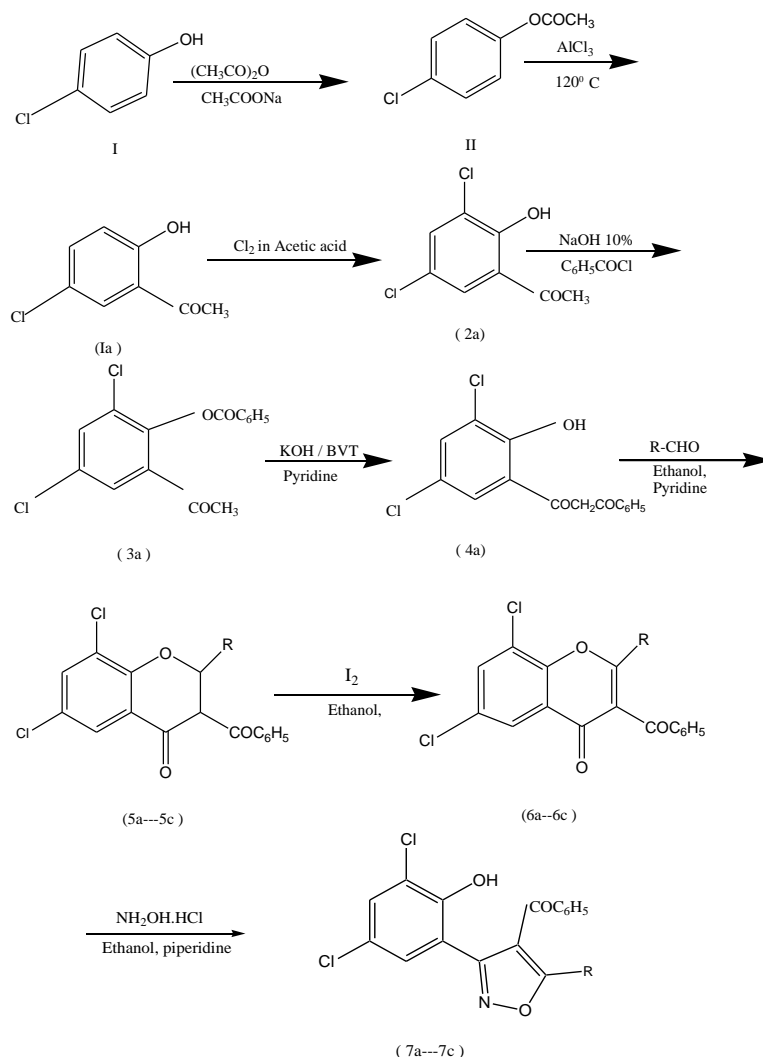
The newly synthesized compounds were characterized on the basis of elemental analysis, molecular determination, U.V., I.R., N.M.R. spectral analysis

Compound (5a)-Yield 75%, M.P. 90°C . Elemental analysis for $\text{C}_{22}\text{H}_{13}\text{O}_5\text{NCl}_2$: Found C = 59.68, H = 2.86, N = 3.10. Calculated C = 59.72, H = 2.94, N = 3.16% UV spectrum (EtOH), λ_{max} -364 nm ($n \rightarrow \pi^*$) IR (cm^{-1}) 3050.5 (C-H stretching in Ar) 1611.4 (C=O), 1473.9 (C-NO₂), 1278 (C-O), 1182.6 (C-O) 717.7 cm^{-1} (C-Cl). ^1H NMR spectrum (400 MHz, CDCl_3), δ ppm 6.75 (1H, d, -CH-CH) 6.9 (1H, d, -CH-CH), 6.875 -8.712 (11H, m, Ar-H) (Silverstein et al. 1991).

Compound (5b)-Yield 70%, M.P. 120°C . Elemental analysis for $\text{C}_{22}\text{H}_{13}\text{O}_3\text{Cl}_3$: Found C = 61.10, H = 2.96, Calculated C = 61.18, H = 3.01, %. UV spectrum (EtOH), λ_{max} -319 nm ($n \rightarrow \pi^*$) IR (cm^{-1}) 2928.6 (C-H stretching in Ar) 1612.6 (C=O), 1427.7 (C-H in Ar), 1086.5 (C-O), 764.6 cm^{-1} (C-Cl). ^1H NMR spectrum (400 MHz, CDCl_3), δ ppm 6.76 (1H, d, -CH-CH) 6.79 (1H, d, -CH-CH), 6.926-8.315 (11H, m, Ar-H).

Compound (5c)-Yield 75%, M.P. 155°C . Elemental analysis for $\text{C}_{20}\text{H}_{18}\text{O}_3\text{Cl}_2$: Found C = 63.54, H = 4.50, Calculated C = 63.66, H = 4.77, %. UV spectrum (EtOH), λ_{max} -363 nm ($n \rightarrow \pi^*$) IR (cm^{-1}) 3068.7 (C-H stretching in Ar) 2866.4 (C-H stretching in Ar), 2866.4 (C-H in $-(\text{CH}_2)_3-$), 1689.5 (C=O), 1605.8 (C-H stretching in Ar) 1457.7 (-CH₃ Bending), 1286.3 (C-O in ether), 705.4 cm^{-1} (C-Cl). ^1H NMR spectrum (400 MHz, CDCl_3), δ ppm 0.90 (3H, t, $(\text{CH}_2)_3\text{-CH}_3$) 1.25 (2H, m $(\text{CH}_2)_2\text{-CH}_2\text{-CH}_3$) 1.50 (2H, t, $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$) 2.65 (2H, t, $\text{CH}_2\text{-(CH}_2)_2\text{-CH}_3$) 6.88 (1H, d, C-H), 6.93 (1H, d, C-H) 7.00 -8.225 (7H, m, Ar-H).

Compound (6a)-Yield 80%, M.P. 164°C . Elemental analysis for $\text{C}_{22}\text{H}_{11}\text{O}_5\text{NCl}_2$: Found C = 59.00, H = 2.30, N = 3.00, Calculated, C = 60.00, H = 2.50, N = 3.18, %).



Where R = C₆H₅-NO₂, C₆H₅-Cl, (CH₂)₃-CH₃

Figure 1. Synthesis of novel compounds of isoxazoles

Compound (6b)-Yield 75%, M.P. 168°C. Elemental analysis for C₂₂H₁₁O₃Cl₃: Found C = 61.14, H = 2.20 Calculated C = 61.18, H = 2.56%. UV spectrum (EtOH), λ_{max}—345 nm (n → π*) IR (cm⁻¹), 2917.8 (C-H stretching in Ar), 1639.5 (C=O), 1604.1 (>C=O), 1091.1 (-C-O in ether), 768.2 cm⁻¹ (-C-Cl). ¹H NMR spectrum (400 MHz, CDCl₃), δppm 6.848-8.319 (11H, m, Ar-H).

Compound (6c)-Yield 80%, M.P. 162°C. Elemental analysis for C₂₀H₁₆O₃Cl₂: Found C = 63.60, H = 4.10, Calculated C = 64.00, H = 4.27, %. UV spectrum (EtOH), λ_{max} 301nm (n → π*), IR (cm⁻¹) 2942.5 (Ar -CH), 2851.7 (CH str. in alkane), 1637.9 (>C=O), 1431.7 (-CH₂bending), 1345.8 (-CH₃ bending) 1250.2 (-C-O in ether) 765.5 cm⁻¹ (-C-Cl). ¹H NMR spectrum (400 MHz, CDCl₃), δppm 1.285 (3H, s, -(CH₂)₃-CH₃), 2.050 (2H, qui, (-CH₂)₂-CH₂-CH₃), 2.808 (2H, m, H₂-CH₂-CH₂-CH₃), 2.839 (2H, t, CH₂-(CH₂)₂-CH₃)

Compound (7a)-Yield 80%, M.P. 148°C. Elemental analysis for C₂₂H₁₂O₅N₂Cl₂: Found C = 57.80, H = 2.40,

N=6.00, Calculated C = 58.02, H = 2.64, N=6.15 %).

Compound (7b)-Yield 85%, M.P. 160°C. Elemental analysis for C₂₂H₁₂O₃NCl₃: Found C = 59.15, H = 2.50, N=3.00, Calculated C = 59.39, H = 2.69, N=3.14 %. UV spectrum (EtOH), λ_{max} 312nm, IR (cm⁻¹) 3021 (O-H stretching), 1623 (>C=O), 1464.1 (>C=N), 1275.1 (C-O-N), 763 cm⁻¹ (-C-Cl). ¹H NMR spectrum (400 MHz, acetone), δppm 6.915-8.129 (11H, m, Ar-H).

Compound (7c)-Yield 80%, M.P. 165°C. Elemental analysis for C₂₀H₁₇O₃NCl₂: Found C = 61.40, H = 4.20, N=3.40 Calculated C = 61.53, H = 4.35, N=3.60, %. UV spectrum (EtOH), λ_{max} 303nm (n → π*), IR (cm⁻¹) 3351.4 (O-H streraching), 2938.5 (C-H in alkane), 1641.4 (>C=O), 1444.1 (-CH₂ bending), 1351.5 (-CH₃ bending), 1219 (C-O-N), 768.7 cm⁻¹ (-C-Cl). ¹H NMR spectrum (400 MHz, acetone), δppm 1.282 (3H, t, -(CH₂)₃-CH₃), 2.050 (2H, s, -CH₂-CH₂-CH₂-CH₃), 2.845 (2H, s, -CH₂-CH₂-CH₂-CH₃), 2.874 (2H, s, -CH₂-CH₂-CH₂-CH₃), 6.910 to 8.122 (8H, m, Ar-H).

Growth promoting activities on some flowering plants

The experimental set up of the study was divided into seed treatment and field experiment. (i) Seed treatment: with a view to safeguard dormant seed's potential from harmful external agencies, the seed of the test plants were treated by test compounds before sowing. (ii) Field experiment: pre-germinated quality seeds of *P. rhoeas*, *C. officinalis*, *G. tristis*, *G. aristata*, *D. chinensis*, and *Iberis* sp. were procured from genuine agricultural agencies.

The beds of black cotton soil, 2.5 x 2.5m size were prepared on an open field. The sowing of seeds of all six flowering plants under examination was done in beds and earthen pots separately by conventional methods and irrigated as and when required. The plants from each bed and pot were divided into two groups, i.e., A and B which were designated as 'control' and 'treated' group plants respectively. The plants from group B were sprayed with the solution of test compounds at fortnightly intervals. The field experiments were conducted to compare the treated plants of group B with untreated plants of controlled group

A. In this context, the observation was recorded on 15, 30, 45, 60, 75 and 90 days after sowing; corresponding to early vegetative, late vegetative, flowering, pod filling and pod maturation stages, with special reference to number of leaves and height of shoots. The results of field's experiments with test compounds are tabulated in Table 1.

Data presented in Table 1 clearly indicates that shoot heights of *P. rhoeas*, *C. officinalis*, *G. tristis*, *G. aristata*, *D. chinensis*, and *Iberis* sp. up to 45 days did not show any significant increase. However, the shoot heights increased to a remarkable extent from 60 days onwards after sowing, and it continued with the same drift up to 90 days in almost all the treated plants as compared to the plants of control group. This trend of substantial increase in shoot height geared up in *P. rhoeas* and *C. officinalis* right from the second week of the experiment. It has been found that control group plants overshadowed this trend in the third observation only in the plants *P. rhoeas* and *C. officinalis* treated with compound 4a.

Table 1. Activity of the test compounds (4a), (5a), (6a), (7a)

Periodicity of the observation (in days)	Poppy (<i>P. rhoeas</i>)				Calendula (<i>C. officinalis</i>)				Gladiolus (<i>G. tristis</i>)				Gaillardia (<i>G. aristata</i>)				Pink (<i>D. chinensis</i>)				Candytuft (<i>Iberis</i> sp)			
	Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves		Shoot height		No. of leaves	
	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
Activity of the test compound 1-(2'-hydroxy-3', 5'-dichlorophenyl)-3-phenyl-1, 3-propanedione (4a)																								
15	3	3	9	10	2	1	9	4	2	1	1	1	4	3	4	5	2	2	4	4	3	2	9	5
30	7	5	15	15	4	7	18	18	6	5	2	2	6	8	15	8	5	4	10	8	6	4	15	20
45	10	10	20	25	8	10	30	30	10	9	4	2	8	15	30	20	7	8	15	16	8	7	45	40
60	12	12	22	30	10	16	55	55	15	16	5	3	12	18	50	38	10	12	25	29	12	11	60	70
75	16	17	30	47	13	20	80	85	20	20	6	4	16	20	70	60	13	16	34	41	15	15	100	105
90	20	23	50	78	15	21	100	115	22	21	6	4	20	21	105	95	18	20	50	63	18	19	130	150
Activity of the test compound 3-benzoyl-2-(4'-nitrophenyl)-6, 8-dichloroflavanone (5a)																								
15	3	3	9	7	2	2	9	12	2	2	1	1	4	2	4	5	2	2	4	2	3	4	9	10
30	7	6	15	10	4	5	18	28	6	5	2	2	6	5	15	8	5	4	10	6	6	8	15	27
45	10	12	20	20	8	11	30	40	10	9	4	2	8	8	30	20	7	7	15	12	8	12	45	62
60	12	18	22	25	10	15	55	60	15	16	5	5	12	10	50	38	10	9	25	18	12	15	60	100
75	16	22	30	38	13	20	80	100	20	21	6	5	16	12	70	60	13	12	34	26	15	19	100	145
90	20	26	50	48	15	22	100	130	22	25	6	5	20	18	105	80	18	17	50	45	18	24	130	205
Activity of the test compound 3-benzoyl-2-(4'-nitrophenyl)-6, 8-dichloroflavone (6a)																								
15	3	3	9	8	2	3	9	14	2	2	1	1	4	4	4	6	2	3	4	5	3	3	9	8
30	7	7	15	15	4	6	18	30	6	5	2	2	6	6	15	8	5	7	10	12	6	7	15	18
45	10	12	20	38	8	10	30	50	10	11	4	3	8	10	30	27	7	10	15	18	8	12	45	56
60	12	16	22	50	10	14	55	70	15	15	5	3	12	14	50	50	10	15	25	29	12	15	60	98
75	16	20	30	60	13	18	80	90	20	21	6	5	16	18	70	80	13	20	34	45	15	19	100	135
90	20	24	50	100	15	20	100	120	22	23	6	5	20	21	105	140	18	21	50	70	18	23	130	200
Activity of the test compound 3-(2'-hydroxy-3', 5'-dichlorophenyl)-4-benzoyl-5-(4''-nitrophenyl) isoxazole (7a)																								
15	3	2	9	7	2	2	9	10	2	3	1	1	4	3	4	6	2	2	4	3	3	4	9	10
30	7	4	15	12	4	5	18	22	6	10	2	3	6	6	15	14	5	4	10	15	6	6	15	30
45	10	8	20	20	8	8	30	48	10	12	4	3	8	10	30	40	7	8	15	25	8	11	45	50
60	12	14	22	45	10	13	55	77	15	16	5	5	12	15	50	60	10	12	25	49	12	18	60	120
75	16	18	30	60	13	17	80	135	20	20	6	6	16	19	70	90	13	16	34	76	15	21	100	172
90	20	24	50	95	15	20	100	180	22	23	6	7	20	23	105	135	18	20	50	120	18	23	130	210

Note: C = control, T = treated

The treatment of compound 5a showed very positive results in the increase of shoot height in all test plants as compared to control group plants except in the *D. chinensis* plant that has been mentioned in the 2nd observation. The treatment of compound 6a promoted shoot height of test plants to a great extent except in *P. rhoeas* whereas this plant started responding to the treatment of titled compound 6a after 6th week onward only. The same trend was retained by the test plants on treatment with the titled compound 7a.

The data about the foliage of the test plants depicted in Table 1 revealed that there was a remarkable increase in the number of leaves in treated plants as compared to control group plants. However, in the first phase of the experiment, there was no significant difference between treated and control group plants of *P. rhoeas*, and *C. officinalis*. But the fifth week onwards the foliage density gradually increases and it shoots up in the later phase of the study to a considerable extent as compared to the control group plants.

CONCLUSION

The synthesized compounds were screened for their growth promoting activity on some flowering plants viz: *Papaver rhoeas*, *Calendula officinalis*, *Gladiola tristis*, *Gaillardia aristata*, *Dianthus chinensis* and *Iberis* sp. The efforts have been made to examine and analyze the morphology of treated plants. When the comparison of morphological characters was made between those of treated and control groups plants, it was interesting to note that all the plants exhibited significant shoot growth and considerable increase in the number of leaves as compared to those of untreated ones.

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