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Studies on arylfuran derivatives
Part XI. Synthesis, characterisation and biological studies on some Mannich bases carrying 2,4-dichlorophenylfurfural moiety

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Abstract

A series of 3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidine]amino-5-mercapto-1,2,4-triazoles (**3**) are synthesised. Aminomethylation of **3** with formaldehyde and a primary/secondary amine furnished Mannich bases **4** and **5**. Both Schiff bases **3** and Mannich bases **4** and **5** are characterised on the basis of IR, ^{1}H NMR, mass spectral data and elemental analysis. All the newly synthesised compounds are tested for their antibacterial activities. Some of the selected compounds are also tested for their fungicidal and herbicidal properties.

Keywords: Arylfuran derivative; Schiff bases; Mannich bases; Antibacterial, antifungal and herbicidal activities

1. Introduction

In continuation of our studies on arylfuran derivatives [1] and in an attempt to modify the structure of nitrofuran drugs, it was decided to synthesise a series of 1-arylaminomethyl-3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4-triazoles (**4**) and 4-methyl-piperazin-l-yl-methyl-3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4-triazoles (**5**) starting from the respective Schiff bases **3**. All these Mannich bases are screened for their antibacterial activity. Some of the selected compounds are also tested for their antifungal and herbicidal properties. Results of such studies are discussed in this paper.

2. Chemistry

2,4-Dichlorophenylfurfural (**2**) was synthesised through the Meerwein reaction [2]. 3-Alkyl/aryl/aryloxymethyl substituted-4-amino-5-mercapto-1,2,4-triazoles (**1**) were prepared according to a literature method [3,4]. In order to study the structure–activity relationship, a primary amine, 3-chloro-4-fluoroaniline and a secondary amine, i.e. *N*-methylpiperazine were used in the present investigation.

The triazoles **1** were condensed with 2,4-dichlorophenylfurfural (**2**) in the presence of a few drops of concentrated sulfuric acid as a catalyst to produce Schiff bases **3** in good yields. These Schiff bases were then treated with primary/secondary amines in the presence of formaldehyde, in ethanol or dioxane–ethanol to produce Mannich bases **4** and **5** (Scheme 1). The structures of Schiff bases and Mannich bases were established on the basis of elemental analysis, IR, ^{1}H NMR and mass spectral data. The characterisation data of these compounds are given in Tables 1–3, respectively.

The IR spectrum of compound **3f** showed an absorption band at 1610 cm^{-1} indicating the presence of

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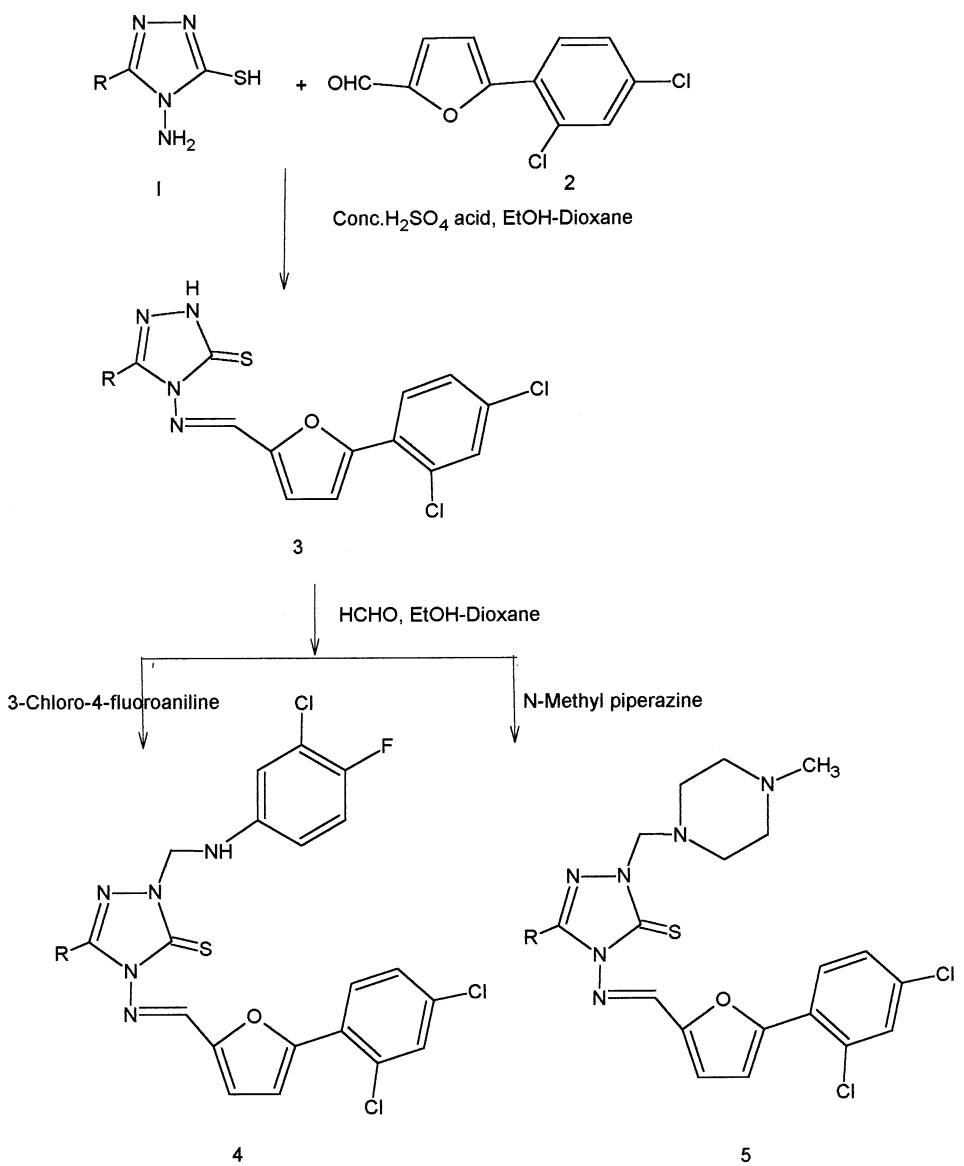
>C=N– in the molecule. The absorption band observed at 3094 cm^{-1} is attributable to the NH–C=S group. IR spectral data of the Schiff bases are given in Table 1.

In the PMR spectrum of Schiff base **3d**, a sharp singlet corresponding to one proton, characteristic of the –N=CH– group, was observed at δ, 10.46. A downfield signal appearing at δ, 13.37 is attributed to the –N=C(SH)– moiety indicating the facile thione–thiol tautomerism. Two β-protons of the furan ring resonated as two doublets at δ, 7.31 ($J = 3.7$ Hz) and δ, 7.16 ($J = 3.7$ Hz), respectively integrating for two protons. The protons of the propyl side chain appeared as a triplet, multiplet and a triplet at δ, 1.04 ($J = 7.4$ Hz), 1.61 ($J = 7.4$ Hz) and 2.8 ($J = 7.5$ Hz), respectively. The signals attributable to the two aromatic protons of the 2,4-dichlorophenyl moiety appeared as a multiplet in the range δ, 7.3–7.5 integrating for two protons, whereas the other aromatic proton appeared as a doublet at δ, 7.94 ($J = 8.3$ Hz).

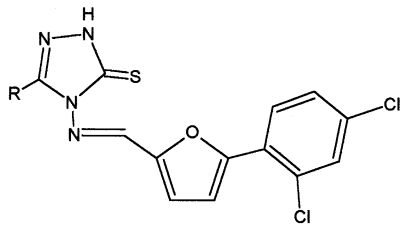
The mass spectra of compound **3f** was found to be fully consistent with the assigned structure. The molecular ion peak for the Schiff base was observed at m/z 478 corresponding to the molecular formula $C_{20}H_{13}Cl_3N_4O_2S$. The base peak however, was observed at m/z 128, which corresponds to the molecular ion of *p*-chlorophenol. A peak observed at m/z 237 indicates the formation of 2,4-dichlorophenylfuronitrile during the fragmentation, characteristic of arylfuran heterocycles and Schiff bases.

In the IR spectrum of the Mannich base (4 h), the absorption band corresponding to >C=N– bond is seen at 1640 cm^{-1}, while the absorption band appearing at



Scheme 1.

Table 1
Characterisation data of 3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4-triazoles (**3a–j**)[a]



3

Comp. no.	R	M.p. (°C)	Yield (%)	Molecular formula	Anal. %N found (Calc.)
3a	H	246–248	82	$C_{13}H_8Cl_2N_4OS$	16.46 (16.57)
3b	CH_3	220–222	84	$C_{14}H_{10}Cl_2N_4OS$	15.81 (15.90)
3e	C_2H_5	177–179	80	$C_{15}H_{12}Cl_2N_4OS$	15.26 (15.30)
3d	C_3H_7	170–172	76	$C_{16}H_{14}Cl_2N_4OS$	14.61 (14.3)
3e	Ph	232–234	88	$C_{19}H_{12}Cl_2N_4OS$	14.46 (14.52)
3f	4-Chlorophenoxymethyl	205–207	94	$C_{20}H_{13}Cl_3N_4O_2S$	11.23 (11.17)
3g	2-Chlorophenoxymethyl	193–195	90	$C_{20}H_{13}Cl_3N_4O_2S$	11.08 (11.17)
3h	4-Chloro-3-methyl-phenoxymethyl	192–194	96	$C_{21}H_{15}Cl_3N_4O_2S$	11.43 (11.38)
3i	2,4-Dichlorophenoxymethyl	211–213	89	$C_{20}H_{12}Cl_4N_4O_2S$	10.86 (10.93)
3j	3,4-Dimethyl-phenoxymethyl	214–215	83	$C_{22}H_{18}Cl_2N_4O_2S$	11.73 (11.86)

[a] IR (KBr, ν cm^{-1}): **3f**, 3094 (NH/SH), 1610 (C=N); **3h**, 3092 (NH/SH), 1608 (C=N); **3i**, 3096 (NH/SH), 1610 (C=N). MS: **3f**, m/z 478 (M^+, 12%), m/z 128 (*p*-chlorophenol, 100%), m/z 237 (2,4-dichlorophenyl furonitrile, 45%). ^{1}H NMR ($CDCl_3$): **3d**, δ, 10.46 (s, 1H, –N=CH–), 13.37 (s, 1H, –N=C–SH), 7.31 (d, 1H, furan 4H, $J = 3.7$ Hz), 7.16 (d, 1H, furan 3H, $J = 3.7$ Hz), 7.3–7.5 (m, 2H, aromatic H), 7.94 (d, 1H aromatic H, $J = 8.3$ Hz), 1.04 (t, 3H –CH_3 of propyl group, $J = 7.4$ Hz), 1.61 (m, 2H –CH_2– of propyl group, $J = 7.4$ Hz), 2.8 (t, 2H, –CH_2–. of propyl group, $J = 7.5$ Hz).

1280 cm^{-1} could be attributed to the >C=S functional group. A sharp absorption band at 3360 cm^{-1} indicates the presence of an NH group in this compound.

In the PMR spectrum of compound **4e**, the –N–CH_2–NH– protons resonate as a singlet at δ, 6.30 integrating for two protons and a singlet at δ, 7.08 corresponding to the –NH proton. The signal due to the –N=CH– proton was seen as a singlet at δ, 10.07. The two β-protons of the furan ring appeared as two doublets at δ, 7.46 ($J = 3.8$ Hz) and 7.19 ($J = 3.8$ Hz), respectively, integrating for two protons. A multiplet at δ, 7.3–7.9 corresponds to the eleven aromatic protons.

The mass spectrum of compound **5c** showed a molecular ion peak at m/z 479 corresponding to the protonated molecular ion. A base peak was seen at m/z 237 indicating the formation of a molecular ion of 2,4-dichlorophenylfuronitrile during the fragmentation. A fragmentation peak at m/z 113, confirmed the formation of *N*-methyl piperazinylmethyl cation, which is a characteristic feature of Mannich bases.

3. Experimental

Melting points were determined by the open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. PMR spectra were recorded ($CDCl_3$/$CDCl_3$ + DMSO-d_6 mixture) on a Bruker AC-300F (300 MHz) NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a VG Micromass mass spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates.

*3.1. 3-Substituted 4-[5-(2,4-dichlorophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4-triazoles (**3**)*

To a suspension of 2,4-dichlorophenylfurfuraldehyde (**2**; 10 mmol) in dioxane (15 ml), an equimolar amount of the corresponding aminomercaptotriazole (**1**) was added. The suspension was heated until a clear solution was obtained. Then, a few drops of concentrated sulphuric acid were added and the solution was heated under reflux for 3–4 h on a water bath. The precipitated solid was filtered off and recrystallized from a mixture of ethanol and dioxane (2:1) to yield the title compounds **3**.

*3.2. 1-Arylaminomethyl/piperazin-1-yl-methyl-3-substituted-4-[5-(2,4-dichlorophenyl)-2.furfurylidene]-amino-5-mercapto-1,2,4-triazoles (**4** and **5**)*

The Schiff base (**3**; 10 mmol) was dissolved in a mixture of ethanol and dioxane (2:1). Then, formalde-

hyde (40%, 1.5 ml) and primary/secondary amine (10 mmol) in ethanol were added to this solution. The mixture was stirred for 2–3 h and kept overnight at room temperature (r.t.). The resulting solid that separated was collected by filtration, washed with ethanol and recrystallised from a mixture of ethanol–dioxane (2:1) to yield the title compounds **4** and **5**.

4. Biological activity

4.1. Antibacterial activity

The newly synthesised compounds, **3a**–**j**, **4a**–**j** and **5a**–**j** were screened for their in vitro, antibacterial activities against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis* according to the serial dilution method [5]. Furacin was used as a standard drug for comparison. Most of the compounds have shown antibacterial activities lower than that observed for the reference drug.

4.2. Antifungal activity

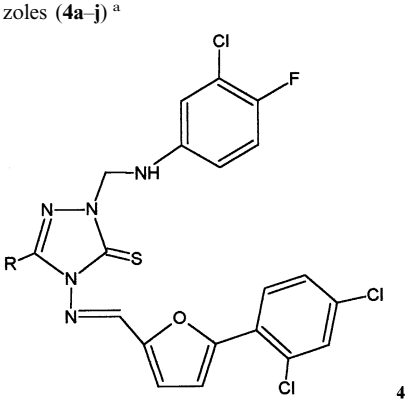
Eight selected compounds were screened for their fungicidal action [6] against *Fusarium sp*, *Alternaria solani* and *Plasmopara viticola* under laboratory conditions and the results are given in Table 4.

4.2.1. Conclusion

From the above data it is evident that the Schiff bases and their Mannich derivatives showed antifungal activity against *Fusarium sp*, *Alternaria solani* to a lesser degree when compared to the standard drug Hexaconazole. However all the compounds were inactive against *Plasmopara viticola*.

The data as indicated in Table 6 reveals that weed control rating was 6 in the case of Paraquat and 8 in respect of Glyphosate, indicating their proven performance as post-emergence herbicides. The rating in respect of all the test compounds was 1 as in the case of the untreated control. These results indicate that the test compounds do not have post-emergence herbicidal activities.

Table 2
Characterisation data of 1-(3-chloro-4-fluoroanilino)methyl-3-substituted-4-[5-(2,4-dichlorophenyl)-2- furfurylidene]amino-5-mercapto-1,2,4-triazoles (**4a**–**j**) [a]

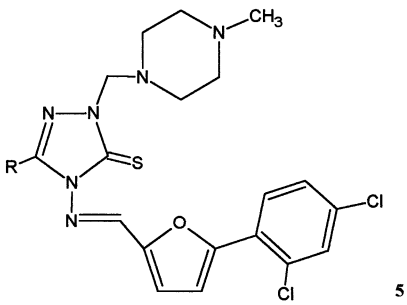


4

Comp. no.	R	M.p. (°C)	Yield (%)	Molecular formula	Anal. %N found (Calc.)
4a	H	250–252	72	$C_{20}H_{13}Cl_3FN_5OS$	14.04 (14.14)
4b	CH_3	200–202	74	$C_{21}H_{15}Cl_3FN_5OS$	13.64 (13.75)
4c	C_2H_5	172–174	66	$C_{22}H_{17}Cl_3FN_5OS$	13.28 (13.38)
4d	C_3H_7	140–142	68	$C_{23}H_{19}Cl_3FN_5OS$	12.94 (13.03)
4e	Ph	215–217	73	$C_{26}H_{17}Cl_3FN_5OS$	12.08 (12.22)
4f	4-Chlorophenoxymethyl	193–195	88	$C_{27}H_{18}Cl_4FN_5O_2S$	11.13 (11.02)
4g	2-Chlorophenoxymethyl	170–172	73	$C_{27}H_{18}Cl_4FN_5O_2S$	10.84 (11.02)
4h	4-Chloro-3-methyl-phenoxymethyl	180–182	86	$C_{28}H_{20}Cl_4FN_5O_2S$	10.64 (10.78)
4I	2,4-Dichlorophenoxymethyl	165–167	82	$C_{27}H_{17}Cl_5FN_5O_2S$	10.32 (10.46)
4j	3,4-Dimethyl-phenoxymethyl	183–185	74	$C_{29}H_{23}Cl_5FN_5O_2S$	11.06 (11.13)

[a] IR (KBr, ν cm^{-1}): **4h**, 3360 (NH), 1640 (C=N), 1280 (C=S); **4g**, 3362 (NH str.), 1642 (C=N), 1280 (C=S); **4i**, 3364 (NH), 1644 (C=N), 1281 (C=S). MS: **4i**, M^+ is not observed, m/z 237 (2,4-dichlorophenyl furonitrile, 100%), m/z 175 (2,4-dichloroaryloxymethyl cation, 65.2%), m/z 158 (3-chloro-4-fluoro-anilinomethyl cation, 6.5%), ^{1}H NMR ($CDCl_3$ + DMSO-d_6): **4e**, δ, 10.07 (s, 1H –N=CH–), 7.46 (d, 1H, furan 4H, $J = 3.8$ Hz), 7.19 (d, 1H, furan 3H, $J = 3.8$ Hz), 7.3–7.9 (m, 11H, aromatic H), 6.3 (s, 2H >N–CH_2–NH–), 7.08 (s, 1H, –NH).

Table 3
Characterisation data of 4-methyl-piperazin-1-yl-methyl-3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurylidene]amino-5-mercapto-1,2,4-triazoles (**5a**–**j**) [a]



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Comp. no.	R	M.p. (°C)	Yield (%)	Molecular formula	Anal. %N found (Calc.)
5a	H	182–184	68	$C_{19}H_{20}Cl_2N_6OS$	18.52 (18.67)
5b	CH_3	191–193	70	$C_{20}H_{22}Cl_2N_6OS$	18.01 (18.01)
5c	C_2H_5	163–165	72	$C_{21}H_{24}Cl_2N_6OS$	17.43 (17.57)
5d	C_3H_7	124–126	60	$C_{22}H_{26}Cl_2N_6OS$	16.98 (17.07)
5e	Ph	184–186	65	$C_{25}H_{24}Cl_2N_6OS$	15.84 (15.97)
5f	4-Chlorophenoxymethyl	138–140	82	$C_{26}H_{25}Cl_3N_6O_2S$	14.12 (14.23)
5g	2-Chlorophenoxymethyl	130–132	68	$C_{26}H_{25}Cl_3N_6O_2S$	14.13 (14.23)
5h	4-Chloro-3-methyl-phenoxymethyl	140–142	81	$C_{27}H_{27}Cl_3N_6O_2S$	13.78 (13.90)
5I	2,4-Dichlorophenoxymethyl	180–182	73	$C_{26}H_{24}Cl_4N_6O_2S$	13.32 (13.46)
5j	3,4-Dimethyl-phenoxymethyl	160–162	68	$C_{28}H_{30}Cl_2N_6O_2S$	14.28 (14.46)

[a] IR (KBr, ν cm^{-1}): **5f**, 1640 (C=N), 1272 (C=S). ^{1}H NMR (300 MHz, $CDCl_3$), **5h**, δ, l0.40 (s, 1H N=CH), 7.29 (d, 1H, furan 4H, $J = 3.7$ Hz), 7.12 (d, 1H, furan 3H, $J = 3.7$ Hz), 6.78–7.75 (m, aromatic H, 6H), 5.18 (s, 2H –O–CH_2–), 5–17 (s, 2H, N–CH_2–N), 2.86 (s, 3H –NCH_3), 2.29 (s, 4H, CH_2–N–CH_2), 2.27 (s, 4H CH_2–N(CH_3)–CH_2), 1.76 (s, 3H, CH_3). MS: **5c**, m/z 479 (M^+, 18%), m/z 237 (2,4-dichlorophenyl furonitrile, 100%), m/z 113 (*N*-methylpiperazinylmethyl cation, 23.2%).

Table 4
Antifungal activity data of Schiff and Mannich bases

Comp. no.	Initial inoculum size disc of 8 mm (fungal growth in mm)		Infection of *Plasmopara* (%)
	Fusarium	*Alterania*	
3f	79	60	100
3g	77.5	66	100
3h	76	56	100
3i	80	58	100
4f	75	52	100
4g	75	57	100
4h	72	49	100
4I	73	51	100
Blank	77	52	100
Standard			
1. Hexaconazole	8		
2. Akomin		8	10
Check	85	90	100

From these studies, it is concluded that the test compounds are not effective for pre-emergence and post-emergence weed management.

4.3. Herbicidal activities

Trials were carried out to evaluate the pre- and post-emergence herbicidal effects of eight test compounds **3f**, **3g**, **3h**, **3i**, **4f**, **4g**, **4h** and **4i**. All the test compounds were provided as 5% EC formulation: A blank formulation was also provided. Details of the trials are given below.

4.3.1. Evaluation of test compounds for pre-emergence herbicidal effect

A mixture of 5 mg seeds of each of the annual grass,

Table 5
Effect of test compounds on pre-emergence weed control

Treatment	Dosage (l ha^{-1})	No. of weed seed germinated (Days after treatment)		
		7	14	21
Test compound **3f** 5EC	1000 ppm (0.50 kg a.i.)	14	20	24
Test compound **3g** 5EC	1000 ppm (0.50 kg a.i.)	14	19	26
Test compound **3h** 5EC	1000 ppm (0.50 kg a.i.)	15	18	27
Test compound **3i** 5EC	1000 ppm (0.50 kg a.i.)	12	20	25
Test compound **4f** 5EC	1000 ppm (0.50 kg a.i.)	16	18	27
Test compound **4g** 5EC [a]	1000 ppm (0.50 kg a.i.)	13	19	25
Test compound **4h** 5EC	1000 ppm (0.50 kg a.i.)	15	17	27
Test compound **4i** 5EC	1000 ppm (0.50 kg a.i.)	16	18	26
Blank (DMF–xylene)		15	19	28
Atrazine 50 WP	1.50 (kg a.i.)	0	0	2
Pendimethalin 30 EC	1.00 (kg a.i.)	0	0	3
Untreated control		15	19	26

[a] Test compound **4g** 5EC formulation had precipitated in the container at the time of imposing.

Digitaria sanguinalis and the broadleaf weed, *Amaranthus viridis* was sown in pots one day prior to imposing treatment. The soil was moistened with light irrigation. The test compounds and two standard herbicides, Atrazine and Pendimenthalin that are recommended for pre-emergence weed control were applied one day after sowing the seeds. Treatments were imposed using a hand-held sprayer. Volume of spray fluid was equivalent to 750 l ha^{-1} hectare.

Observations were recorded on the number of seeds germinated at periodic intervals. The results are summarised in Table 5.

Germination of seeds was not noticed in pots treated with Atrazine and Pendimethalin. This indicates their proven performance as pre-emergence herbicides. In the pots treated with all the test compounds, germination of seeds was noticed as in the case of the untreated control. Differences between the number of seeds germinated under different test compounds treatments were marginal. These results indicate that pre-emergence herbicide activity was not significant in any of the test compounds.

4.3.2. Evaluation of test compounds for post-emergence herbicidal effect

A trial was carried out in open plots in the field infested completely with the grasses, *Digitaria sanguinals* and *Cynodon dectylon* and the broadleaf weeds, *Amanthus viridis*, *Euphorbia hirta* and *Parthenium hysterophorus*. There were 12 treatments including eight test compounds, one blank, two post-emergence weed controls and Glyphosate, which are recommended for post-emergence weed control and an untreated control. All the treatments were imposed in plots of 1 m^2 area using a hand-held sprayer. Volume of spray fluid was at the rate of 500 l ha^{-1}.

Visual observations on the percentage weed control were recorded on a scale of 1 to 10, 10 being complete control in terms of desiccation/necrosis of weeds.

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Table 6
Effects of test compounds on post-emergence weed control

Treatment	Dosage (l ha^{-1})	No. of weed seed germinated (Days after treatment)				
		5	10	15	20	25
Test compound **3f** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **3g** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **3h** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **3i** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **4f** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **4g** 5EC [a]	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **4h** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Test compound **4i** 5EC	1000 ppm (0.50 kg a.i.)	1	1	1	1	1
Blank (DMF+ xylene)		1	1	1	1	1
Gyphosate 41 SC	1.22 (kg a.i.)	2	5	7	8	8
Paraquat 24 WSC	0.48 (kg a.i.)	3	4	6	6	6
Untreated control		1	1	1	1	1

[a] Test compound **4g** 5EC formulation had precipitated in the container at the time of imposing treatment.

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