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Original article

Synthesis of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo(thiadiazoles and thiadiazines) as anti-inflammatory and molluscicidal agents

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ABSTRACT

A series of fused and non fused 1,2,4-triazoles with (2,4-dichlorophenoxy) moiety are prepared utilizing 3-((2,4-dichlorophenoxy)methyl)-4-amino-4*H*-1,2,4-triazole-5-thiol (**3**). The latter on reaction with carboxylic acids, ethylchloroformate, ethylcyanoacetate and sodium nitrite gives five membered fused triazole derivatives **4a**–**d**, **5**, **6**, **7** and **10**, respectively. The six membered heterocycles **11**, **12** and **14** are prepared by cyclization of compound **3** with phenacyl bromide, chloroacetic acid and α-bromoketone respectively. Most of the newly synthesized compounds were screened for their anti-inflammatory and molluscicidal activities. The compounds **4b**, **4d**, **11** and **14** showed potent anti-inflammatory activities in dose dependent manner while compounds **3**, **4b**, **8** and **10** exhibited promising molluscicidal activities.

1. Introduction

1,2,4-Triazole derivatives are known to exhibit antibacterial, antifungal [1], antitubercular [2], anticancer [3], anticonvulsant [4], anti-inflammatory [5], analgesic [6], and molluscicidal properties [7–10]. Among the pharmacological profiles of 1,2,4-triazoles, their antimicrobial, anticonvulsant, and antidepressant properties seem to be best documented. The arrangement of three basic nitrogen atom in the triazole ring induces antiviral activity in the compounds containing a triazole ring [11]. The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates including H_1/H_2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety, and sedatives agents [12]. Some of the modern day drugs with triazole nucleus are Ribavirin (antiviral agent), Alprazolam (anxiolytic agent), Fluconazole, Itraconazole (antifungal agent) and Rizatriptan (antimigrane agent).

The ambient nucleophilic centers present in 3-substituted-4-amino-5-mercapto-1,2,4-triazoles render them as useful synthons for the synthesis of various *N*-bridged heterocycles. Moreover, synthesis of triazole fused to other heterocycles has attracted attention widely due to their diverse applications.

Prompted by these observations, it was contemplated to synthesize some newly *N*-bridged heterocycles containing (2,4-dichlorophenoxy) moiety (which possess an excellent herbicidal activity) [13] with a view to explore their potency as better chemotherapeutic agents. Some newly synthesized compounds were screened for the anti-inflammatory and molluscicidal activities.

2. Results and discussion

2.1. Chemistry

3-((2,4-Dichlorophenoxy)methyl)-4-amino-4*H*-1,2,4-triazole-5-thiol (**3**), was prepared according to a methodology involves the condensation of 2,4-dichlorophenoxyacetic acid hydrazide (**1**) with carbon disulfide and potassium hydroxide to yield the potassium dithiocarbazate **2** which, after *s*-alkylation with methyl iodide, underwent ring closure with an excess of hydrazine to produce the aminothiol **3** in good yield [14].

Cyclocondensation of the SH and NH_2 functions of **3** with aromatic carboxylic acids and oxalic acid in the presence of phosphoryl chloride, to give 3-((2,4-dichlorophenoxy)methyl)-6-aryl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **4a**–**d** and bis(3-(2,4-dichlorophenoxy)methyl)-6,6′-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole **5**, respectively. The structure of the isolated products **4a**–**d** and **5** was elucidated on the basis of

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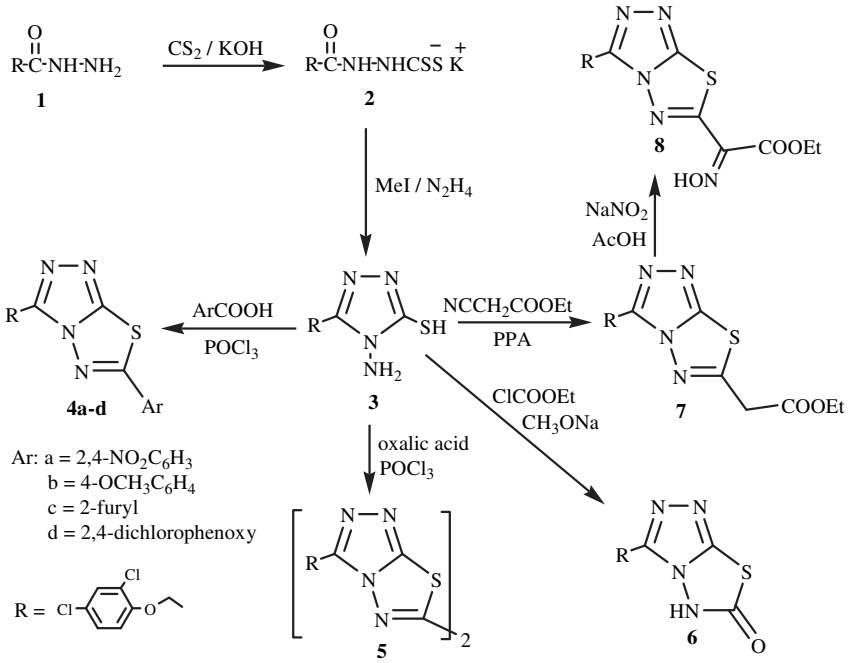


Scheme 1. Synthesis of triazolo-thiadiazole derivatives **4a–d**–**8**.

their spectral (MS, IR and ^{1}H NMR) and elemental analyses data. (cf. Scheme 1 and Tables 1 and 2).

Compound **3** reacted with ethylchloroformate in the presence of sodium methoxide affording a cyclized product, 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-6(5*H*)-one (**6**) in good yield. Treatment of **3** with ethylcyanoacetate in polyphosphoric acid afforded triazolo[3,4-*b*][1,3,4]thiadiazole derivative **7** in good yield. Nitrosation of **7** with sodium nitrite in the presence of acetic acid, afforded hydroxyimino derivative **8** in fairly good yield.

When compound **3** was treated with some aromatic aldehydes namely, benzaldehyde, 2,4-dichlorobenzaldehyde and 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde; a Schiff base derivatives **9a–c** were obtained in good yields. Reaction of **3** with sodium nitrite in hydrochloric acid, give *s*-triazolo[3,4-*b*][1,3,4]thiatriazole **10**.

3-((2,4-Dichlorophenoxy)methyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**11**) was successfully achieved on treatment of **3** with equimolar amounts of phenacyl bromide in refluxing absolute ethanol. Structure **11** was deduced from microanalytical and spectral data.

Chloroacetic acid in the presence of sodium acetate reacts with **3** affording in one step 3-((2,4-dichlorophenoxy)methyl)-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4] thiadiazine-6-(7*H*)-one (**12**). On the other hand, when **3** was treated with α-bromopropenone derivative **13** [15] in the presence of potassium hydroxide in ethanol, the arylidenetriazolothiadiazine **14** was formed in good yield. Both spectral and elemental analyses were in accord with the suggested structure. (cf. Scheme 2 and Tables 1 and 2).

Table 1
Physical constants of newly synthesized compounds.

Compd. no.	Yield (%)	m.p. (°C)	Mol. form. (Mol. wt)	Microanalysis		
				C	H	N
4a	(77)	215–217	$C_{16}H_8Cl_2N_6O_5S$ (467.24)	41.13	1.73	17.99
				41.22	1.88	17.80
4b	(70)	247–249	$C_{17}H_{12}Cl_2N_4O_2S$ (407.27)	50.13	2.97	13.76
				50.01	2.79	13.86
4c	(60)	207–209	$C_{14}H_8Cl_2N_4O_2S$ (367.21)	45.79	2.20	15.26
				45.87	2.12	15.38
4d	(55)	176–178	$C_{17}H_{10}Cl_4N_4O_2S$ (476.16)	42.88	2.12	11.77
				42.79	2.20	11.68
5	(60)	162–164	$C_{20}H_{10}Cl_4N_8O_2S_2$ (600.29)	40.02	1.68	18.67
				40.13	1.76	18.58
6	(50)	187–189	$C_{10}H_6Cl_2N_4O_2S$ (317.15)	37.87	1.91	17.67
				37.94	1.84	17.74
7	(40)	178–180	$C_{14}H_{12}Cl_2N_4O_3S$ (387.24)	43.42	3.12	14.47
				43.33	3.04	14.58
8	(60)	184–186	$C_{14}H_{11}Cl_2N_5O_4S$ (416.24)	40.40	2.66	16.83
				40.32	2.73	16.77
9a	(70)	118–120	$C_{16}H_{12}Cl_2N_4OS$ (379.26)	50.67	3.19	14.77
				50.59	3.26	14.68
9b	(60)	149–151	$C_{16}H_{10}Cl_4N_4OS$ (448.15)	42.88	2.25	12.50
				42.94	2.17	12.58
9c	(77)	252–254	$C_{27}H_{18}Cl_2N_6O_2S$ (561.44)	57.76	3.23	14.97
				57.68	3.30	14.88
10	(65)	171–173	($C_9H_5Cl_2N_5OS$ (304.16)	35.54	2.32	23.03
				35.60	2.25	23.11
11	(55)	214–216	$C_{17}H_{12}Cl_2N_4OS$ (391.27)	52.18	3.09	14.32
				52.11	3.17	14.26
12	(60)	179–181	$C_{11}H_8Cl_2N_4O_2S$ (331.18)	39.89	2.43	16.92
				39.96	2.37	16.88
14	(70)	235–237	$C_{37}H_{22}Cl_2N_6O_3S$ (701.58)	63.34	3.16	11.98
				63.41	3.09	11.92

2.2. Pharmacological screening

2.2.1. Molluscicidal activity

The toxicity of compounds **3**, **4a–d**, **5**, **6**, **7**, **8**, **9a–c**, **10**, **11**, **12** and **14** toward *Biomphalaria alexandrina* snails was evaluated. An insight inspection of the results listed in (Table 3) shows that compounds **3**, **4b**, **8** and **10** have high effect on the snails but all the other compounds have moderate to low effects on the snails, and they all showed very weak activity below 5 ppm. A data obtained showed promising results especially compounds possess a triazolothiatriazole moiety and hydroxyimino residue and this data was in a good agreement with previous reports [7–10].

A comparison of the molluscicidal activity of the new compounds reported here with the international standard 2′,5-dichloro-4-nitrosalicylanilide (Bayluscide) [16,17]; showed that our compounds are still far inferior as molluscicidal agents.

Table 2
Mass, IR, ^{1}H NMR spectral data of newly synthesized compounds.

Compd. no.	Mass (*m*/*z*) (%)	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm) (DMSO-d_6)
4a	[M]$^+$, 466 (30)	1600 (C=N), 2970, 2950 (CH aryl)	δ 5.77 (s, 2H, CH_2 phenoxy), 7.45–7.60 (m, 6H, Ar-H)
4b	[M]$^+$, 406 (60)		δ 3.64 (s, 3H, CH_3), 5.70 (s, 2H, CH_2 phenoxy), 7.16–7.93 (m, 7H, Ar-H)
4c	[M]$^+$, 366 (38)	1594 (C=N). 2975, 2960 (CH aryl)	δ 5.68 (s, 2H, CH_2 phenoxy), 6.85–6.88 (m, 1H, furyl H-4), 7.45–7.63 (m, 4H, Ar-H and furyl H-3), 8.12–8.16 (m, 1H, furyl H-5)
4d	[M]$^+$, 474 (45)		δ 5.69 (s, 2H, CH_2 phenoxy), 5.74 (s, 2H, CH_2 phenoxy), 7.41–7.71 (m, 6H, Ar-H)
5	[M]$^+$, 598 (50)		δ 5.60 (s, 2H, CH_2 phenoxy), 5.65 (s, 2H, CH_2 phenoxy), 7.21–7.62 (m, 6H, Ar-H)
6	[M]$^+$, 316 (63)	1640 (CO), 3120 (NH)	δ 5.23 (s, 2H, CH_2 phenoxy), 7.31–7.58 (m, 3H, Ar-H), 13.87 (s, 1H, NH)
7	[M]$^+$, 386 (35)		δ 1.28 (m, 3H, CH_3), 4.15 (m, 2H, CH_2ester), 4.41 (s, 2H, CH_2), 5.71 (s, 2H, CH_2 phenoxy), 7.31–7.72 (m, 3H, Ar-H)
8	[M]$^+$, 415 (35)		δ 1.31 (t, 3H, CH_3), 4.24 (q, 2H, CH_2ester), 5.21 (s, 2H, CH_2 phenoxy), 7.35–7.81 (m, 3H, Ar-H), 10.63 (s, 1H, OH)
9a	[M]$^+$, 378 (63)	1268–1248 (C=S), 1590 (C=N), 2955, 2980 (CH aryl), 3210 (NH)	δ 5.40 (s, 2H, CH_2 phenoxy), 7.38–7.77 (m, 8H, Ar-H), 8.12 (s, 1H, N=CH), 11.85 (br.s, 1H, NH)
9b	[M]$^+$, 446 (74)		δ 5.48 (s, 2H, CH_2 phenoxy), 7.43–7.93 (m, 6H, Ar-H), 8.00 (s, 1H, N=CH), 10.84 (br.s, 1H, NH)
9c	[M]$^+$, 560 (70)		δ 5.45 (s, 2H, CH_2 phenoxy), 7.35–7.64 (m, 13H, Ar-H and furan H-2), 8.10 (s, 1H, N=CH), 9.24 (s, 1H, pyrazole H-3), 10.47 (br.s, 1H, NH)
10	[M]$^+$, 303 (54)		δ 5.23 (s, 2H, CH_2 phenoxy), 7.31–7.58 (m, 3H, Ar-H)
11	[M]$^+$, 390 (80)		δ 4.45 (s, 2H, thiadiazin CH_2), 5.51 (s, 2H, CH_2 phenoxy), 7.39–7.95 (m, 8H, Ar-H)
12	[M]$^+$, 330 (70)	1686 (CO), 3200 (NH)	δ 5.22 (s, 2H, thiadiazinone CH_2), 5.63 (s, 2H, CH_2 phenoxy), 7.32–7.60 (m, 3H, Ar-H), 13.86 (br.s, 1H, NH)
14	[M]$^+$, 700 (50)		δ 5.34 (s, 2H, CH_2 phenoxy), 7.14–8.11 (m, 19H, Ar-H and methylene H)

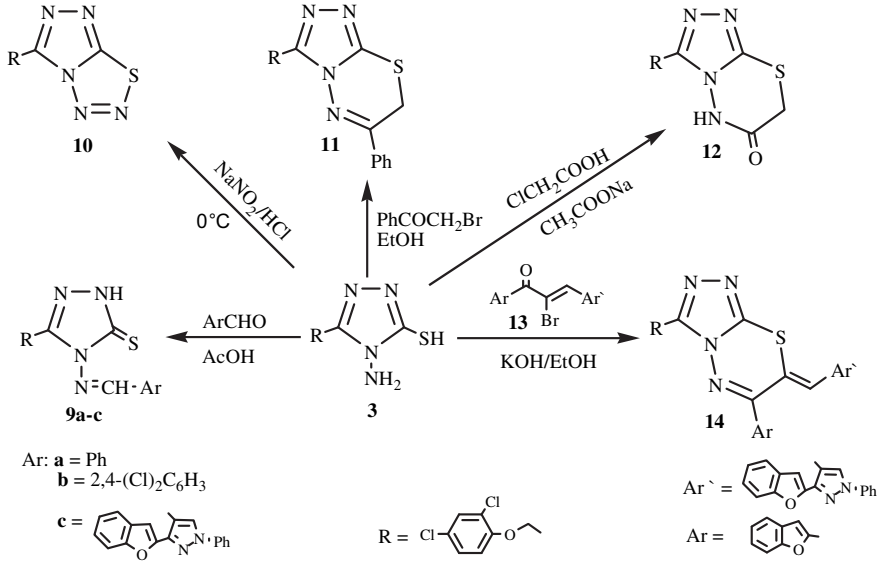
2.2.2. Anti-inflammatory activity

The anti-inflammatory activity of the synthesized compounds (Table 4) was evaluated by carrageenan-induced paw oedema method of Winter and Nuss [18]. Compounds **4b**, **4d**, **11**, **14** showed significant anti-inflammatory effect, which protected rats by 36–56% from inflammation other tested compounds did not show any significant anti-inflammatory effect which might be permeated to their solubility issue (DMSO is not physiologically accepted solvent for in vivo experiment; and accordingly it was used with limitation). From the view point of structure activity relationship (SAR), it is clear that the triazolothiadiazole derivatives having 2,4-dichlorophenoxy **4d** and 4-methoxyphenyl **4b** at C-6 position possess highest activity compared with indomethacin. Moreover, the triazolothiadiazine derivatives having 2,4-dichlorophenoxy at C-3 and phenyl or benzofuryl at C-6 positions having significant activity. The obtained results were in accordance with previous reports [19,20].

3. Experimental

3.1. General

All melting points were determined on an Electrothermal 9100 digital melting point apparatus. IR, ^{1}H NMR and mass spectra were recorded on: IR spectra (KBr): Pye-Unicam SP-1100. ^{1}H NMR spectra: Jeol GLM EX 270 MHz FT NMR spectrophotometer, DMSO-d_6, TMS as internal standard, chemical shift in δ (ppm). Mass spectra: 70 eV, Varian MAT 311 A. Elemental analysis (in accord with the calculated values) was carried out in the microanalytical unit, Faculty of Science, Cairo University. Yields are not optimized. Anti-inflammatory activities were carried out at pharmacology unit, National Research Centre. 2,4-Dichlorophenoxyacetic acid hydrazide **1** and 4-amino-5-((2,4-dichlorophenoxy) methyl)-4*H*-1,2,4-triazole-3-thiol **3** were prepared as previously described [14].



Scheme 2. Synthesis of triazolo-thiadiazine derivatives.

Table 3
Molluscicidal activity of compounds **3**, **4a–d** and **5–14** on *Biomphalaria alexandrina* snails (10 snails by concentrations) under Laboratory conditions and after 24 h exposure.

Compd. No.	Different concentration used in (ppm)		
	1	5	10
3	0	6	10
4a	0	1	5
4b	0	3	7
4c	0	1	6
4d	0	0	3
5	0	2	6
6	0	2	5
7	0	0	4
8	0	3	8
9a	0	0	3
9b	0	1	5
9c	0	0	4
10	0	5	10
11	0	3	6
12	0	2	5
14	0	1	5
Bayluscide	10	10	10

3.2. General procedure for synthesizing of (*4a–d*)

A mixture of **3** (10 mmol) and aromatic acids (10 mmol) in the presence of $POCl_3$ (15 mL) was refluxed for 2–3 h. After removal of the excess of $POCl_3$ under reduced pressure, the residual added to crushed ice and the mixture stirred at room temperature for 1 h. During this time the solution was gradually neutralized with (Na_2CO_3), the solid product was filtered off, washed with water, dried and recrystallized from appropriate solvent to afford the title compounds.

3.2.1. 3-((2,4-Dichlorophenoxy)methyl)-6-(2,4-dinitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (*4a*)

The compound was obtained from the reaction of 2,4-dinitrobenzoic acid (10 mmol), as white solid (EtOH).

3.2.2. 3-((2,4-Dichlorophenoxy)methyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (*4b*)

The compound was obtained from the reaction of 4-methoxybenzoic acid (10 mmol), as white solid (EtOH).

3.2.3. 3-((2,4-Dichlorophenoxy)methyl)-6-(furan-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (*4c*)

The compound was obtained from the reaction of furan-2-carboxylic acid (10 mmol), as white solid (EtOH).

3.2.4. 3,6-Bis((2,4-dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazole (*4d*)

The compound was obtained from the reaction of 2,4-dichlorophenoxyacetic acid (10 mmol), as white solid (EtOH).

3.3. 3-((2,4-Dichlorophenoxy)methyl)-6-(3-((2,4-dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (*5*)

Compound **5** was synthesized from **3** (20 mmol) and oxalic acid (10 mmol) in a manner similar to that described for **4a–d** as white solid (EtOH).

3.4. 3-((2,4-Dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazol-6(5H)-one (*6*)

To **3** (10 mmol), sodium methoxide (10 mmol) in (50 mL) methanol and ethylchloroformate (10 mmol) was added. The reaction mixture was refluxed for 5 h, then evaporated under vacuum, the solid obtained washed with water and recrystallized to yield **6** as white solid (EtOH).

3.5. Ethyl-2-(3-((2,4-dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazol-6-yl)acetate (*7*)

A mixture of **3** (10 mmol) and ethylcyanoacetate (10 mmol) in PPA (15 mL) was stirred at 60 °C for 6 h. After cooling the reaction mixture was added to crushed ice and the mixture stirred at room temperature for 1 h. During this time the solution was gradually neutralized with $NaHCO_3$. The solid product was filtered off, washed with water, dried and recrystallized to give **7** as white solid (EtOH).

3.6. Ethyl 2-(3-((2,4-dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)-2-(hydroxyimino)acetate (*8*)

To a solution of **7** (10 mmol) in (20 mL) acetic acid, aqueous sodium nitrite (20 mmol) was added portionwise, with stirring at 0–5 °C, over a period of 20 min. After 3 h, the reaction mixture was poured onto water, a precipitate was formed, filtered off, and crystallized to give **8** as white solid (EtOH).

3.7. General procedure for synthesizing of (*9a–c*)

A solution of **3** (10 mmol) in glacial acetic acid (10 mL) was allowed to react with the appropriate aldehydes (10 mmol) under reflux for 1 h. The reaction mixture was then cooled and the

Table 4
Anti-inflammatory activity of compounds **3**, **4a–d** and **10–14** against carrageenan-induced rat paw oedema over 4 h.

Group	(% Inhibition of oedema) ± S.E.			
	1 h	2 h	3 h	4 h
3	(49.99675)[a] ± 8.852533	(60.30075)[a] ± 6.318443	(102.8511)[a] ± 6.44741	(81.74565)[a] ± 13.4234
4a	(32.16216)[a] ± 5.542188	(66.06168)[a] ± 16.70769	(68.04117)[a] ± 8.771818	(63.95059)[a] ± 6.462582
4b	(26.74506)[b] ± 1.651259	(46.22208)[b] ± 10.17494	(56.33506)[b] ± 9.240293	(44.33871)[b] ± 9.676857
4c	(51.37782)[a] ± 12.46712	(54.62069)[a] ± 12.6645	(99.24333)[a] ± 13.43806	(93.97222)[a] ± 20.89291
4d	(26.94604)[b] ± 2.755955	(48.39525)[b] ± 7.749848	(63.15481)[b] ± 7.584049	(58.48116)[b] ± 6.456058
10	(70.78083)[a] ± 25.75219	(94.79833)[a] ± 22.14129	(108.482)[a] ± 37.94043	(74.03251)[a] ± 19.40933
11	(27.65508)[b] ± 2.601153	(45.62023)[b] ± 5.10145	(60.42211)[b] ± 7.215277	(48.51348)[b] ± 10.54937
14	(29.71395)[b] ± 5.692312	(41.31841)[b] ± 6.448136	(59.66482)[b] ± 12.636069	(35.77512)[b] ± 9.791311
Cont	(48.54701) ± 4.955791	(66.60562) ± 9.022303	(72.88156) ± 10.1965	(72.97924) ± 14.61699
Indomethacin	(24.80194)[b] ± 15.32791	(20.97271)[b] ± 17.03966	(26.28741)[b] ± 15.27344	(20.19146)[b] ± 17.59208

Values represent the mean ± S.E. of six animals for each group. Data were analyzed by One-way *T*-test using Indomethacin as anti-inflammatory standard agent.
[a] Represents not significance level at $P < 0.05$.
[b] Represents the significance level at $P < 0.05$.

precipitated arylidene derivatives were filtered off, washed with water, dried and recrystallized from appropriate solvent to afford the title compounds.

*3.7.1. 5-((2,4-Dichlorophenoxy)methyl)-4-(benzylideneamino)-2H-1,2,4-triazole-3(4H)-thione (**9a**)*

The compound was obtained from the reaction of benzaldehyde (10 mmol), as white solid (EtOH).

*3.7.2. 4-(2,4-Dichlorobenzylideneamino)-5-((2,4-dichlorophenoxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (**9b**)*

The compound was obtained from the reaction of 2,4-dichlorobenzaldehyde (10 mmol), as white solid (EtOH).

*3.7.3. 4-((3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methyleneamino)-5-((2,4-dichlorophenoxy)methyl)-2H-1,2,4-triazole-3(4H)-thione (**9c**)*

The compound was obtained from the reaction of 3-(benzofuran-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (10 mmol), as white solid (MeOH).

*3.8. 4-((2,4-Dichlorophenoxy)methyl)-[1,2,4]triazolo[4,3-d]-[1,2,3,4]thiatriazole (**10**)*

A solution of **3** (10 mmol) in HCl (50 mL) was cooled to 0 °C and a cold solution of sodium nitrite (10 mmol) in water (10 mL) was gradually added. The reaction mixture was kept at 0–5 °C with stirring for 2 h, left overnight and diluted with water where upon precipitation took place. The solid that precipitated was collected and recrystallized to give **10** as white solid (EtOH).

*3.9. 3-((2,4-Dichlorophenoxy)methyl)-6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**11**)*

A mixture of **3** (10 mmol) and phenacyl bromide (10 mmol) in absolute ethanol (50 mL) was refluxed for 8 h. The solvent was then removed by distillation and the remaining residue was washed with water, filtered, dried and recrystallized to give **11** as white solid (EtOH).

*3.10. 3-((2,4-Dichlorophenoxy)methyl)-5H-[1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazin-6(7H)-one (**12**)*

To **3** (10 mmol) in acetic acid (50 mL), chloroacetic acid (20 mmol) and fused sodium acetate (15 mmol) were added. The reaction mixture was refluxed for 6 h, cooled and the solid obtained filtered off, washed with water, and recrystallized to give **12** as white solid (EtOH).

*3.11. 3-((2,4-Dichlorophenoxy)methyl)-7-((3-(benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-6-(benzofuran-3-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (**14**)*

A mixture of **3** (10 mmol), 1,3-diaryl-2-bromo-2-propen-1-ones 13 (10 mmol), and ethanolic potassium hydroxide (15 mmol) was refluxed in ethanol (15 mL) for 8 h. The precipitated solid was filtered off, washed with water, and recrystallized to give **14** as white solid (AcOH).

4. Biological screening

4.1. Molluscicidal activity tests

The molluscicidal activity tests were carried out for each compound under investigation. *B. alexandrina* snails (ca. 7 mm shell diameter) were collected from the field (water canals) and maintained under laboratory conditions for a period of 10 days before the test and fed daily by lettuce leaves. Three concentrations of each compound under investigation were prepared ranging from 1 to 10 ppm. The required amount of the compound under investigation was mixed thoroughly with few drops of Tween 20 and 2 mL of DMSO to render the compounds completely soluble, followed by addition of the appropriate volume of untreated raw water (taken directly from the Nile River or its subsidiary branches/canals) to get a homogeneous suspension with the requisite concentration and placed in glass jar vessels 15 × 25 × 20 cm dimensions fitted with air bubblers. Ten snails were used in each experiment and maintained in the test solution under laboratory conditions at 25 °C for 24 h. Each experiment was repeated three times, and the mean number of killed snails was taken for each concentration (Table 3). A control group was taken by placing 10 snails in water containing few drops of Tween 20 and 2 mL of DMSO. Bayluscide was used as a reference molluscicidal agent. These bioassays are in accordance with the W.H.O guidelines [21] slightly modified by using two mixed solvents to dissolve the compounds.

4.2. Methodology of anti-inflammatory activity

1 h after drug oral administration, rats weighting ≈200 gm each were injected subplanter into the hind left paw with 1 mg carrageenan dissolved in 100 mL physiological solution. Paw volumes were measured every hour using standard fluid displacement procedures (plethysmometer) by dipping the hind left paw in 0.45% saline solution every 1 h interval for total of 4 h. The percent change in paw volume compared to base line measurement was taken as the criteria of comparison. Indomethacin was used as an internal standard anti-inflammatory agent. The method adopted resembles essentially that described by Winter et al. (Table 4).

5. Conclusions

In summary, a series of new *s*-triazole and fused triazole derivatives carrying the 2,4-dichlorophenoxy moiety (2,4-D) could be synthesized and evaluated for their anti-inflammatory and molluscicidal activities. Some of triazolothiadiazole and triazolothiadiazine showed highly significant anti-inflammatory effect, which protected rats by 36–56% from inflammation as compounds **4b**, **4d**, **11**, **14** comparable to the standard (Indomethacin). The compounds **4b**, **8** and **10** showed potent molluscicidal activities as compared to the standard molluscicidal agent (Bayluscide).

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