Journal of Molecular Structure 1236 (2021) 130305

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Synthesis, structural elucidation and larvicidal activity of novel arylhydrazones

Nefisath P[a,b], Jagadeesh Prasad Dasappa[b,*], Haripriya B[c], Deepak Chopra[c], Katharigatta N. Venugopala[d,e], Pran Kishore Deb[f], Raquel M. Gleiser[g], Viresh Mohanlall[e], Rajendra Maharaj[h], Shashiprabha[a], Vishwanatha Poojary[a]

[a] Post Graduate Department of Chemistry, Sri Dharmasthala Manjunatheshwara College (Autonomous), Ujire, 574240, India,
[b] Department of Chemistry, Mangalore University, Mangalagangothri, India
[c] Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal By-pass Road, Bhauri, Bhopal 462 066, Madhya Pradesh, India
[d] Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al-Ahsa, 31982, Kingdom of Saudi Arabia
[e] Department of Biotechnology and Food Technology, Durban University of Technology, Durban, 4001, South Africa
[f] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Philadelphia University, PO Box 1, Amman, 19392, Jordan
[g] CREAN-IMBIV (UNC-CONICET), Av. Valparaíso s.n., Córdoba, Argentina and FCEFyN, Universidad Nacional de Córdoba, Av. Vélez Sársfield 299, Córdoba, 5000, Argentina
[h] Office of Malaria Research Unit, South African Medical Research Council, Peter Mokaba Ridge, Overport, Durban, 4091, South Africa

ARTICLE INFO

Article history:
Received 14 January 2021
Revised 2 March 2021
Accepted 13 March 2021
Available online 18 March 2021

Keywords:
Hydrazone
Febuxostat
Larvicidal
Single-crystal X-ray
Anopheles arabiensis
Carbohydrazide

ABSTRACT

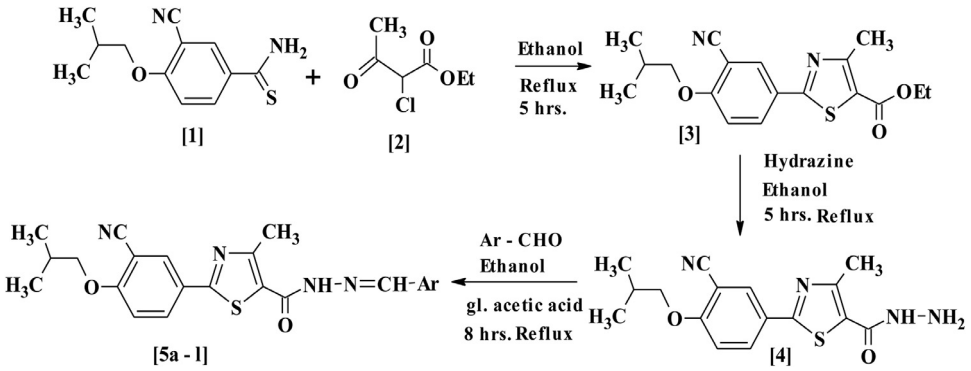
The present study focuses on a series of novel hydrazones of 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]-4-methyl-1,3-thiazole-5-carbohydrazide (**5a-l**) for their larvicidal activity against *Anopheles arabiensis*. The synthesis of the title compounds was achieved by the conventional reflux method, and structures of the novel compounds were ascertained by FT-IR, NMR (^{1}H &^{13}C), LC-MS, and elemental analysis. Compound (**5l**) was studied by single crystal X-ray diffraction for intra and intermolecular interactions. Title compounds (*E*)-2-(3-cyano-4-isobutoxyphenyl)-*N*'-(4-fluoro-3-phenoxybenzylidene)-4-methylthiazole-5-carbohydrazide (**5a**) and (*E*)-*N*'-(4-Chlorobenzylidene)-2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carbohydrazide (**5g**) emerged as promising larvicidal agents against *Anopheles arabiensis.*

1. Introduction

Malaria is an infectious disease spread by infected *Anopheles* mosquitoes. Mosquitoes alone transmit diseases to more than 700 million people annually [1]. Mosquito's immature stages complete their development in standing water in a range of different habitats, depending on the species [2]. Naturally, the abundance of adult mosquitoes depends upon the various other environmental factors such as temperature, rainfall patterns, soil and land cover, as well as the density of larval stages in the habitats [3-7]. Killing mosquitoes at the larval stage is one of the main strategies used to control mosquito-borne diseases [8]. At present, mosquito larvicidal activity depends primarily on the use of synthetic larvicides. As the mosquito larvae are confined to their aquatic habitat, they are highly susceptible to vector control measures, because, unlike adults, they cannot develop behavioral resistance to avoid interventions [9-11]. In turn, it should be noted that, repeated use of larvicides results in toxic effects to humans, non-target organisms, environment and the development of resistance in mosquito populations [12]. These problems highlight the urgent need for the development of more effective, safe and target-specific new larvivides. Literature review reveals that hydrazone derivatives exhibit larvicidal activity [13-14], antimicrobial activity [15-18], analgesic and anti-inflammatory activity [19-22], anticancer activity [23-27], CNS activity [28-29], antiprotozoal activity [30-32] and cardioprotective & antiplatelet activity [33-34]. It is well documented in the literature that nitrogen/sulfur-containing heterocyclic compounds exhibit larvicidal activities [35-37]. There are a number of commercially available drugs which bear hydrazone as core active moiety like, Nifuroxazide, an oral nitrofuran antibiotic used to treat colitis & diahrrhoea [38], Nitrofurantoin, used as an antibiotic medication to treat bladder infections [39], Furazolidone, a nitrofuran antibacterial agent and monoamine oxidase inhibitor [40], Nitrofurazone, a topical antibiotic ointment [41]. Prompted by these findings

* Corresponding author.
E-mail address: jprasad2003@gmail.com (J.P. Dasappa).

https://doi.org/10.1016/j.molstruc.2021.130305
0022-2860/



Scheme 1. Synthetic scheme for the construction of arylhydrazones (5a-i) and (5j-l).

and in continuation of our search for heterocyclic compounds which have antimosquito [42], and larvicidal activity [43-44], a series of hydrazones of 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazides have been synthesized from 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carboxylate (Febuxostat ester). Febuxostat is a xanthine oxidase inhibitor used for treating gout [45] caused by excessive levels of uric acid in the blood called hyperuricemia [46-47] and sold under the brand names Uloric & Adenuric. In the present work all synthesized hydrazone derivatives were characterized and evaluated for larvicidal activity against *Anopheles arabiensis*. Compound (**5l**) is confirmed by the single crystal X-ray method and studied for its possible intra and intermolecular interaction.

2. Experimental

Laboratory grade chemicals, acquired from Aldrich or Merck were used as received without further purification to synthesize all compounds. Melting points of the novel compounds were recorded in a thermoelectric apparatus: Gallenkamp type, using an open capillary tube method and are uncorrected. The reaction was monitored by TLC method using silica gel coated on the aluminum sheet (Merck$^{60}F_{254}$) with appropriate solvent and visualized under UV light chamber. Infrared (IR) spectra were recorded on a Nicolet 170 SX FT-IR spectrometer (region 4000–500 cm^{-1}), using potassium bromide (KBr) pellets and the frequencies are expressed in cm^{-1}. ^1H NMR was recorded on "Agilent-NMR", VNMRS-400, 400 MHz NMR Spectrometer and ^{13}C NMR was recorded on "Agilent-NMR", VNMRS-400, 100 MHz NMR Spectrometer, using tetramethyl silane as an internal standard and dimethyl sulfoxide-d_6 (DMSO–d_6) as a solvent. Chemical shift values δ are represented in ppm with respect to tetramethylsilane. Coupling constants *J* are given in Hz and multiplicities are reported as singlet (s), doublet (d), triplet (t), broad singlet (bs) and multiplet (m). LC-MS was recorded on Synapt G2 High Detection Mass Spectrometry, Waters, USA. Elemental analysis was done using Thermoflash EA 1112 series CHNS – O – analyzer. Single crystal X-ray Diffraction study was accomplished using Bruker APEX II diffractometer equipped with a CCD detector using monochromated MoKα radiation (λ= 0.71073 Å).

2.1. General procedure for the synthesis of ethyl 2-(3-cyano-4-isobutoxyphenyl)−4-methylthiazole-5-carboxylate (3) [48]

To the solution of 3-cyano isobutoxybenzothioamide (1) (0.006 mol) in ethanol, ethyl-2-chloroacetoacetate (2) (0.014 mol) was added and refluxed for five hours. The reaction mass was cooled to 0–5 °C. The solid separated was filtered, washed with chilled ethanol and dried to obtain intermediate ethyl 2-(3-cyano-4-isobutoxyphenyl)−4-methylthiazole-5-carboxylate (3). The synthetic step for the construction of intermediate (3) is presented in scheme 1.

*2.2. General procedure for the synthesis of 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide (4)*

A solution of ethyl 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carboxylate (3) (0.01 mol) in ethanol (20 mL) was refluxed with hydrazine monohydrate (10 mL) for five hours. Ethanol was distilled off completely and quenched with crushed ice to get the crude product of the parent compound, 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide (4). The crude compound was filtered, washed with cold water, dried and recrystallized from ethanol to obtain the pale yellow compound in 99% yield. The detailed synthetic scheme is depicted in Scheme 1.

*2.3. General procedure for the synthesis of hydrazones of 2-[3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide (5a-l)*

*2.3.1. 2- [3-*Cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide* ***(4)***

(0.01 mol) in ethanol (10 mL) was treated with various substituted aromatic aldehydes and refluxed for 8 h in the presence of few drops of glacial acetic acid. The solid obtained was filtered, washed with chilled ethanol, dried, and recrystallized from ethanol. The synthetic route is represented in Scheme 1. The physicochemical characteristics of hydrazones of (*E*)−2-(3-cyano-4-isobutoxyphenyl)-*N*'-(substituted-phenoxybenzylidene)−4-methyl thiazole-5-carbohydrazide (**5a-i**) and (*E*)−2-(3-cyano-4-isobutoxyphenyl)−4-methyl-*N*'-((5-(substituted-furan-2-yl)methylene)thiazole-5-carbohydrazide (**5j-l**) are tabulated in Table 1.

2.4. Spectral data

*2.4.1. (*E*)−2-(3-Cyano-4-isobutoxyphenyl)-*N*'-(4-fluoro-3-phenoxybenzylidene)−4-methyl thiazole-5-carbohydrazide* ***(5a)***

Appearance: Pale yellow solid; FT-IR (KBr, ν_{max}, cm^{-1}): 3161(N–H), 3056(Ar-H), 2960, 2873(C–H), 2225(C≡N), 1656(*C = O*), 1606(*C = N*), 1585(*C = C*); ^1H NMR(400 MHz, DMSO-d_6), δ(ppm): 10.16(bs, 1H, N–H), 8.16(s, 1H, CH=*N*), 7.99(s, 1H, Ar-H), 7.85(s, 1H, Ar-H), 7.49(s, 2H, Ar-H), 7.28(d, 2H, Ar-H), 7.04(s, 3H, Ar-H), 6.94(s,

Table 1
The physicochemical characteristics of arylhydrazones (5a-i) and (5j-l).

SN	Comp. code	Ar-CHO	M.P. (°C)	Yield (%)	Mol. For.	Mol. Wt
1.	5a	4-F-3-OC_6H_5–C_6H_3	138–140	72	$C_{29}H_{25}FN_4O_3S$	528.59
2.	5b	4-OH-3-OCH_3–C_6H_3	230–232	82	$C_{24}H_{24}N_4O_4S$	464.53
3.	5c	3-OH-4-OCH_3–C_6H_3	210–212	76	$C_{24}H_{24}N_4O_4S$	464.53
4.	5d	3,4-$(OCH_3)_2$–C_6H_3	190–192	74	$C_{25}H_{26}N_4O_4S$	478.56
5.	5e	4-NO_2–C_6H_4	196–198	72	$C_{23}H_{21}N_5O_4S$	463.51
6.	5f	2-CH_3–C_6H_4	198–200	90	$C_{24}H_{24}N_4O_2S$	432.53
7.	5 g	4-Cl-C_6H_4	206–208	88	$C_{23}H_{21}ClN_4O_2S$	452.95
8.	5h	4-OH–C_6H_4	218–220	88	$C_{23}H_{22}N_4O_3S$	434.51
9.	5i	4–OCH_3–C_6H_4	186–188	74	$C_{24}H_{24}N_4O_3S$	448.53
10.	5j	5-(2-NO_2–C_6H_4)–2-furaldehyde	186–188	78	$C_{27}H_{23}N_5O_5S$	529.56
11.	5k	5-CH_3–2-furaldehyde	182–184	84	$C_{22}H_{22}N_4O_3S$	422.50
12.	5l	5-NO_2–2-furaldehyde	228–230	86	$C_{21}H_{19}N_5O_5S$	453.47

1H, Ar-H), 3.90(d, 2H, J = 8 Hz, CH_2), 2.85(s, 3H, CH_3), 2.21–2.23(d, 1H, C–H), 1.11(s, 6H, CH_3); ^{13}C NMR(100 MHz), δ(ppm):162.24, 156.89, 132.56, 132.01, 130.62, 129.87, 124.19, 123.57, 120.42, 117.89, 117.74, 117.42, 115.51, 112.62, 102.94, 77.29, 77.03, 76.78, 75.72, 28.18, 19.09; MS (*m/z*): 529 (M^++1); Elemental Analysis: anal. cald. (%) for $C_{29}H_{25}FN_4O_3S$: C: 65.89; H: 4.77; N: 10.60; Found: C: 65.90; H: 4.75; N:10.62.

*2.4.2. (*E*)–2-(3-Cyano-4-isobutoxyphenyl)–4-methyl*-N'*-(4-nitrobenzylidene)thiazole-5-carbohydrazide*
(***5e***)

Appearance: Yellow solid; FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3166(N–H), 3057(Ar-H), 2959, 2873(C–H), 2227(C≡≡N), 1651(*C = O*), 1606(*C = N*), 1580(*C = C*), 1521 & 1430(NO_2 *asym.* & *sym.*); ^{1}H NMR (400 MHz, DMSO–d_6), δ(ppm): 11.94 (bs, 1H, N–H), 8.26(d, 2H, J = 8 Hz, Ar-H), 8.19(s, 1H, CH=*N*), 8.13–8.16(dd, 2H, Ar-H), 7.93(d, 2H, Ar-H), 7.31(d, 1H, J = 8 Hz Ar-H), 3.97(d, 2H, J = 8 Hz, CH_2), 2.71(s, 3H, CH_3), 2.08–2.11(m, 1H, C–H), 1.03(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR (100 MHz): δ (ppm): 162.34, 148.14, 140.66,133.34, 131.60, 128.57, 125.97, 124.49, 115.79, 114.28, 102.12, 75.63, 40.75, 40.55, 40.34, 40.13, 39.93, 39.71, 39.51, 28.04, 19.11; MS (*m/z*): 464(M^++1); Elemental Analysis: anal. cald. (%) for $C_{23}H_{21}N_5O_4S$: C: 59.60; H: 4.57; N:15.11; Found: C: 59.62; H: 4.55; N: 15.12.

*2.4.3. (*E*)–2-(3-Cyano-4-isobutoxyphenyl)–4-methyl*-N'*-(2-methylbenzylidene)thiazole-5-carbohydrazide*
(***5f***)

Appearance: Pale yellow solid;FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3162(N–H), 3052(Ar-H), 2959, 2873(C–H), 2226(C≡≡N), 1655(*C = O*), 1605(*C = N*), 1588(*C = C*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm): 11.62 (bs, 1H, N–H), 8.45(s, 1H, Ar-H), 8.20(s, 1H, CH=*N*), 8.15(d, 1H, J = 8 Hz, Ar-H), 7.89(d, 1H, J = 8 Hz, Ar-H), 7.30–7.35(m, 3H, Ar-H), 7.25(d, 1H, J = 8 Hz, Ar-H), 3.98(d, 2H, J = 8 Hz CH_2), 2.72(s, 3H, CH_3), 2.42(s, 3H, CH_3), 2.06–2.12(m, 1H, C–H), 1.03(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR(100 MHz), δ(ppm): 162.33, 137.35, 133.21, 132.48, 131.60, 131.27, 130.21, 126.75, 126.46, 126.18, 115.80, 114.44, 102.19, 75.69, 40.80, 40.59, 40.38, 40.17, 39.97, 39.76, 39.55, 28.05, 19.26, 19.11; MS (*m/z*): 433(M^++1); Elemental Analysis: anal. cald. (%) for $C_{24}H_{24}N_4O_2S$: C: 66.64; H: 5.59; N: 12.95; Found: C:66.65; H:5.61; N:12.94.

*2.4.4. (*E*)-*N'*-(4-Chlorobenzylidene)–2-(3-cyano-4-isobutoxyphenyl)–4-methylthiazole-5-carbohydrazide*
(***5 g***)

Appearance: Pale yellow solid;FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3161(N–H), 3052(Ar-H), 2959, 2872(C–H of CH_3), 2227(C≡≡N), 164 (*C = O*), 1605(*C = N*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm):11.98(bs, 1H, N–H), 8.35(s, 1H, Ar-H), 8.28–8.30(dd, 1H, Ar-H), 8.17(s, 1H, CH=*N*), 7.87(d, 2H, Ar-H), 7.63 (d, 2H, Ar-H), 7.45(d, 1H, J = 8 Hz, Ar-H), 4.08–4.10(d, 2H, J = 8 Hz CH_2), 2.84(s, 3H, CH_3), 2.17–2.22(m, 1H, C–H), 1.14(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR (100 MHz), δ (ppm): 162.36, 134.97, 133.39, 131.67, 129.47, 129.36, 126.11, 115.82, 114.41, 102.16, 75.66, 40.76, 40.55, 40.35, 40.13, 39.93, 39.72, 39.51, 28.04, 19.12; MS (*m/z*): 453 (M^+), 455 (M^++2); Elemental Analysis: anal. cald. (%) for $C_{23}H_{21}ClN_4O_2S$: C: 60.99; H: 4.67; N: 12.37; Found: C:60.97; H:4.68; N:12.38.

*2.4.5. (*E*)–2-(3-Cyano-4-isobutoxyphenyl)*-N'*-(4-hydroxybenzylidene)–4-methylthiazole-5-carbohydrazide*
(***5 h***)

Appearance: Pale yellow solid;FT-IR(KBr, $\nu_{max,}$ cm^{-1}): 3163(N–H), 3041(Ar-H), 2961, 2840(C–H of CH_3), 2226(C≡≡N), 1656(*C = O*), 1604(*C = N*), 1571(*C = C*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm): 11.73 (bs, 1H, N–H), 10.07(s, 1H, OH), 8.35 (s, 1H, Ar-H), 8.29(d, 1H, J = 8 Hz, Ar-H), 8.11(s, 1H, CH=*N*), 7.71(d, 2H, J = 8 Hz, Ar-H), 7.45(d, 1H, J = 8 Hz, Ar-H), 6.99(d, 2H, Ar-H), 4.09(d, 2H, J = 8 Hz CH_2), 2.85(s, 3H, CH_3), 2.19–2.22(m, 1H, C–H), 1.14(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR(100 MHz), δ (ppm):168.09, 162.23, 161.45, 159.86, 144.55, 133.26, 131.62, 129.57, 126.19, 125.44, 119.42, 116.32, 115.89, 114.28, 102.01, 75.53, 40.63, 40.42, 40.01, 39.59, 39.38, 28.03, 19.15; MS (*m/z*): 435(M^++1); Elemental Analysis: anal. cald. (%) for $C_{23}H_{22}N_4O_3S$: C: 63.58; H: 5.10; N: 12.89; Found: C:63.55; H:5.12; N:12.90.

*2.4.6. (*E*)–2-(3-Cyano-4-isobutoxyphenyl)*-N'*-(4-methoxybenzylidene)–4-methylthiazole-5-carbohydrazide*
(***5i***)

Appearance: Yellow Solid; FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3164(N–H), 3041(Ar-H), 2958, 2935(C–H), 2227(C≡≡N), 1656(*C = O*), 1604(*C = N*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm): 11.61(bs, 1H, N–H), 8.20(s, 1H, CH=*N*), 8.15(d, 1H, J = 8 Hz, Ar-H), 8.02(s, 1H, Ar-H) 7.67(d, 2H, Ar-H), 7.32(d, 1H, J = 8 Hz, Ar-H), 7.02(d, 2H, Ar-H), 3.97(d, 2H, J = 8 Hz, CH_2), 3.806(s, 3H, OCH_3), 2.72(s, 3H, CH_3), 2.06–2.10(m, 1H, C–H), 1.02(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR(100 MHz), δ(ppm):162.31, 161.34, 133.28, 131.62, 129.36, 127.10, 126.24, 115.82, 114.95, 114.43, 102.19, 75.69, 55.82, 40.80, 40.59, 40.38, 40.17, 39.97, 39.75, 39.55, 28.05, 19.11; MS (*m/z*): 449 (M^++1); Elemental Analysis: anal. cald. (%) for $C_{24}H_{24}N_4O_3S$: C: 64.27; H: 5.39; N: 12.49; Found: C:64.28; H:5.40; N:12.51.

*2.4.7. (*E*)–2-(3-Cyano-4-isobutoxyphenyl)–4-methyl*-N'*-((5-(2-nitrophenyl)furan-2-yl)methylene)thiazole-5-carbohydrazide*
(***5j***)

Appearance: Yellow solid;FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3139(N–H), 2926(C–H of CH_3), 2226(C≡≡N), 1651(*C = O*), 1604(*C = N*), 1525 & 1426(NO_2asym. & *sym.*); ^{1}H NMR (400 MHz, DMSO–d_6), δ(ppm): 11.79(bs, 1H, N–H), 8.20(s, 1H, CH=*N*), 8.15(d, 1H, J = 8 Hz Ar-H), 7.88–7.91(m, 3H, Ar-H), 7.69–7.73(m, 1H, Ar-H), 7.58–7.61(m, 1H, Ar-H), 7.22(d, 1H, J = 8 Hz, Ar-H), 7.06(d, 2H, J = 8 Hz furylAr-H), 3.95(d, 2H, J = 8 Hz CH_2), 2.73(s, 3H, CH_3), 2.06–2.09(m,

1H, C–H), 1.01–1.03(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR(100 MHz), δ (ppm): 168.74, 162.18, 150.62, 150.15, 147.38, 133.15, 133.02, 132.50, 131.73, 130.19, 129.42, 126.19, 124.57, 122.65, 119.07, 116.65, 115.86, 113.97, 112.59, 75.47, 40.63, 40.21, 39.79, 39.37, 28.04, 19.37, 19.13; MS (m/z): 530 (M^++1); Elemental Analysis: anal. cald. (%) for $C_{27}H_{23}N_5O_5S$: C: 61.24; H: 4.38; N: 13.22; Found: C:61.25; H: 4.40; N:13.23.

*2.4.8. (E)–2-(3-Cyano-4-isobutoxyphenyl)–4-methyl-*N'*-((5-methylfuran-2-yl)methylene) thiazole-5-carbohydrazide (**5k**)*

Appearance: Pale yellow solid;FT-IR(KBr, $\nu_{max,}$ cm^{-1}): 3150(N–H), 3039(Ar-H), 2966, 2929, 2872(C–H of CH_3), 2235(C≡≡N), 1654(*C = O*), 1606(*C = N*), 1540(*C = C*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm): 11.71 (bs, 1H, N–H), 8.14(d, 2H, J = 8 Hz, Ar-H), 7.85(s, 1H, CH=*N*), 7.32(d, 1H, J = 8 Hz, Ar-H), 6.83(d, 1H, FurylAr-H), 6.26(d, 1H, FurylAr-H), 3.96(d, 2H, J = 8 Hz CH_2), 2.71(s, 3H, CH_3), 2.37(s, 3H, Furyl CH_3), 2.06–2.09(m, 1H, C–H), 1.00–1.02(d, 6H, J = 8 Hz, CH_3); ^{13}C NMR (100 MHz), δ (ppm): 162.29, 154.98, 148.29, 133.02, 131.50, 126.28, 115.79, 115.36, 114.44, 109.09, 109.01, 102.17, 75.69, 40.79, 40.59, 40.38, 39.96, 39.75, 39.54, 28.06, 19.11, 13.84; MS (m/z): 423(M^++1); Elemental Analysis: anal. cald. (%) for $C_{22}H_{22}N_4O_3S$: C: 62.54; H: 5.25; N: 13.26; Found: C:62.56; H:5.27; N:13.27.

*2.4.9. (E)–2-(3-Cyano-4-isobutoxyphenyl)–4-methyl-*N'*-((5-nitrofuran-2-yl)methylene) thiazole-5-carbohydrazide (**5l**)*

Appearance: Dark yellow solid; FT-IR (KBr, $\nu_{max,}$ cm^{-1}): 3118(N–H), 2963, 2876(C–H), 2229(C≡≡N), 1651(*C = O*), 1604(*C = N*), 156(*C = C*), 1505 & 1424(NO_2 *asym.* & *sym.*); ^{1}H NMR(400 MHz, DMSO–d_6), δ(ppm): 12.06(bs, 1H, N–H), 8.15(s, 2H, Ar-H), 7.95(s, 1H, CH=*N*), 7.69(d, 1H, Ar-H), 7.17–7.23(dd, 2H, furylAr-H), 3.97(d, 2H, J = 8 Hz CH_2), 2.69(s, 3H, CH_3), 2.06–2.13(m, 1H, C–H), 1.04(m, 6H, CH_3); ^{13}C NMR (100 MHz), δ (ppm): 162.34, 152.26, 151.93, 133.02, 131.26, 126.10, 115.65, 114.86, 114.07, 102.16, 75.63, 40.75, 40.55, 40.34, 40.13, 39.92, 39.71, 39.51, 28.08, 19.14; MS(m/z): 454(M^++1); Elemental Analysis: anal. cald. (%) for $C_{21}H_{19}N_5O_5S$: C: 55.62; H: 4.22; N: 15.44; Found: C:55.63; H:4.20; N:15.46.

*2.4.10. Crystal growth and single-crystal X-ray crystallographic study of (E)–2-(3-cyano-4-isobutoxyphenyl)–4-methyl-*N'*-((5-nitrofuran-2-yl)methylene)thiazole-5-carbohydrazide (**5l**)*

Single crystal X-ray Diffraction data of the obtained crystals were collected on a Bruker AXS Kappa APEX II diffractometer with Mo Kα radiation (λ= 0.71073 Å) and APEXII [49] software. The temperature was maintained at 100 K using the Oxford Cryostream low-temperature device. The data integration and reduction were performed with SAINT [50] software suit. SADABS [51] software was used for the absorption correction by a multi-scan method. SIR 2014 [52] program was used for solving the crystal structures by direct methods. The crystal structures were refined by a full-matrix least-squares method based on F^2 using SHELXL-2016 [53] embedded in the program suite WinGX [54]. All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to oxygen and nitrogen were located from the difference Fourier map. All other hydrogen atoms were geometrically fixed and isotropically refined using a riding model. PARST [55] and PLATON [56] were used for all the geometrical calculations. The crystal packing analysis was carried out using Mercury 4.2.0 software [57]. The crystallographic details and refinement parameters are listed in Table 2.

Table 2
Crystallographic data and structure refinement parameters for the title compound (*E*)–2-(3-cyano-4-isobutoxyphenyl)–4-methyl-*N*'-((5-nitrofuran-2-yl)methylene)thiazole-5-carbohydrazide (5l).

CCDC Deposition Number	1,986,119
Formula	$C_{21}H_{19}N_5O_5S$
Formula Weight	453.5
Temperature (K)	100
Wavelength (Å)	0.71073
Crystal System	Triclinic
Space Group	*P*-1
Z', Z	1, 2
a (Å)	6.3414(17)
b (Å)	7.9714 (22)
c (Å)	20.8060 (60)
α (°)	81.967(18)
β (°)	84.511(16)
γ (°)	86.979(17)
Volume (A° [3])	1035.82 (31)
Density (g cm^{-3})	1.45
F (000), μ(mm^{-1})	472.0, 0.202
θ (min, max) (°)	2, 29.1
$h_{min, max}$, $k_{min, max}$, $l_{min, max}$	(−8, 7), (−10,10), (−27,28)
Treatment of Hydrogens	Mixed
No. unique ref/obs. Ref.	5109, 2803
No of Parameters	296
R_all, R_obs	0.141, 0.073
wR2_all, wR2_obs	0.175, 0.147
$\Delta\ \rho_{min, max}$(eÅ^{-3})	−0.556, 0.367
G.o.F	0.975

2.5. Theoretical calculations

Hirshfield surface and 2D finger-print plots were generated using CrystalExplorer 17.5 [58].

2.6. Pharmacology

2.6.1. Larvicidal activity

Anopheles arabiensis used in this study was maintained in accordance with the protocol described by WHO (1975) guidelines [59]: mosquitoes were held in an insectary simulating temperature (27.5 °C), humidity (70%) and lighting (12/12) conditions of a malaria-endemic environment. Thirty instar larvae were introduced into a container with a final concentration of 4 µg/mL of a test compound, which was obtained by adding one milliliter of the compound (1 mg/mL) to distilled water (250 mL). Negative control was set up using the solvent (acetone) and distilled water. Temephos, an active emulsified organophosphate larvicidal drug employed in malaria control programs, was used as a positive control. Larvae were fed specially-made cat food that contained a lower oil/fat content. Larval mortality was examined for each container separately for 20 and 48 h. Mortality (expressed as a percentage) was estimated relative to the initial number of larvae exposed. The bioassay was performed in triplicate and the results are summarized in Table 4.

2.6.2. Data analysis

Differences in larval mortality between treatments were assessed with generalized linear models using a binomial link function [60]. *Anopheles arabiensis* mortality was the dependent variable, while the fixed effects were the test compound (test compounds **5a–I** and **5j-l** and both controls) and observation period (24 and 48 h). A p-value < 0.05 was considered statistically significant. Throughout the test, the results are presented as the adjusted mean ± the standard error.

3. Results and discussion

3.1. Chemistry

Synthesis of hydrazones (**5a-l)** was achieved by three-step reactions as shown in the scheme 1. Hydrazones were obtained by condensation of commercially available substituted aromatic aldehydes with the parent compound 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide (**4)** to yield 70–90% after purification. The maximum yield was observed for the title compound (**5f)** at 90%. All the physicochemical characteristics are given in table 1. In the FT-IR spectrum (KBr) of the compound (**5e),** the absorption band at 3166 cm^{-1} corresponds to the secondary amine N–H. The absorption bands appeared at 2959 and 2873 cm^{-1} correspond to aliphatic C–H & aromatic C–H stretching frequencies appeared at 3057 cm^{-1}. The band observed at 2227 cm^{-1} corresponds to the C≡≡Nstretching. The absorption bands at 1651 cm^{-1}, 1606 cm^{-1} and 1580 cm^{-1} are attributed to –NH–*C* = *O*, *C* = *N*, and *C* = *C*, respectively. Bands at 1521 and 1430 cm^{-1} represent asymmetric and symmetric stretching frequencies of the NO_2 group. 400 MHz ^{1}H NMR spectrum (in ppm) of the compound (**5e)**, showed a doublet at δ 1.03 with coupling constant J = 8 Hz and it is attributed to six protons of two CH_3 groups. The single proton of CH appeared as a multiplet at δ 2.08–2.11. A sharp singlet at δ 2.71 corresponds to three protons of the CH_3 group. CH_2 protons appeared as a doublet at δ 3.97 with a coupling constant J = 8 Hz. The proton of phenyl ring at 5-position appeared as doublet at δ 7.31 with coupling constant J = 8 Hz and at 2 & 6-positions appeared as doublet centered at δ 7.93. The two protons of nitrophenyl group at 2 & 6-positions appeared as a doublet of doublet between δ 8.13–8.27, and the other two protons at 3 & 5-positions appeared as a doublet centered at 8.26. The proton of CH=*N* appeared a sharp singlet at 8.19. The NH proton appeared as a broad singlet at δ 11.94. The mass spectrum of the compound (**5e),** showed a molecular ion peak at 464 (M^++1) which is in agreement with its molecular formula, $C_{23}H_{21}N_5O_4S$.

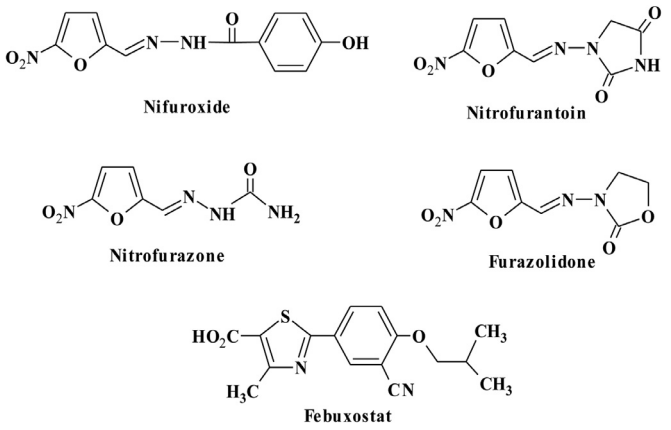


Fig. 1. Structures of commercially available drugs containing hydrazone moiety and Febuxostat.

3.2. Single crystal X-Ray diffraction (SCXRD)

Single crystals of the compound (**5l)** were grown from DMF under the diffusion of diethyl ether at 4 °C, and crystallographic data and structure refinement parameters are tabulated in Table 2. It crystallizes in a centrosymmetric *P*-1 space group with one molecule in the asymmetric unit [Fig. 2].

The geometrical details of all the interactions involved in the crystal packing are given in Table 3.

The crystal packing is majorly stabilized by *C* − *H*•••O and *N* − H4•••N hydrogen bonds, which are supported by weak π•••π interactions. A centrosymmetric molecular tetramer is formed in the *bc* plane by means of bifurcated C17−H17C•••N14/C13 (Symmetry code: 1-x, 1-y, 1-z) and C17−H17B•••O2 (Symmetry code: 1-x, -y, 1-z) hydrogen bonds as shown in Fig. 3.

These molecular tetramers are stacked along *a* axis by the arrangement of the molecules on top of each other in a parallel fashion [Fig. 4]. The layers within the stacks are stabilized by various hydrogen bonds and π•••π interactions. Inversion related molecules are joined via N19−H19•••O2 (Symmetry code: 2-x, -y, 1-z) hydrogen bond. Molecules related by simple translation along

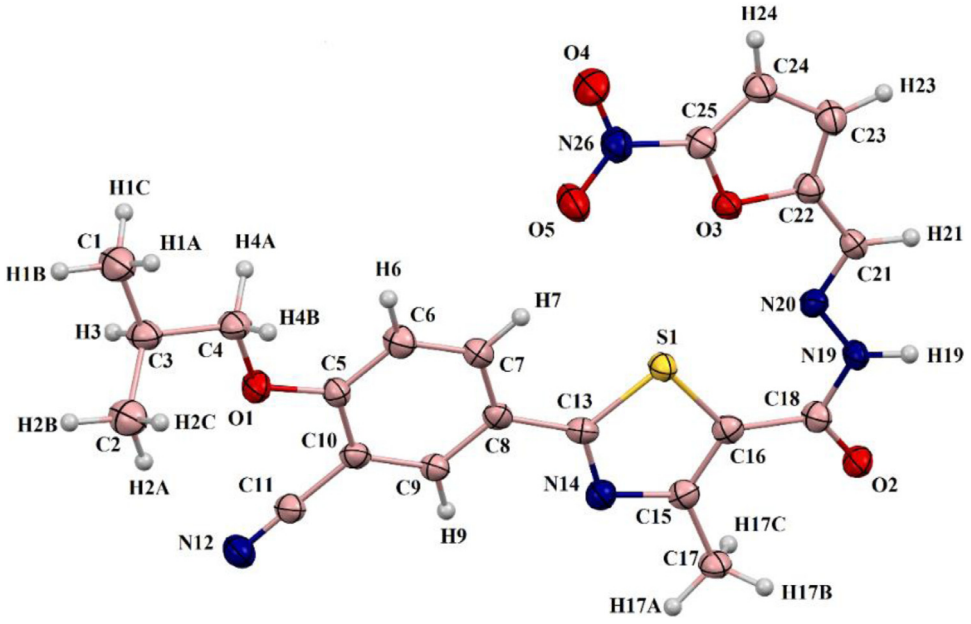


Fig. 2. ORTEP of the compound (5l) drawn with 50% ellipsoidal probability depicting the asymmetric unit.

Table 3
List of interactions in (*E*)−2-(3-cyano-4-isobutoxyphenyl)−4-methyl-*N*'-((5-nitrofuran-2-yl)methylene)thiazole-5-carbohydrazide (**5l**).

Interactions	Symmetry code	D•••A (Å)	H•••A (Å)	*D* − *H*•••A (°)
N19−H19•••O2	2-x, -y, 1-z	2.8410 (7)	1.97	178
C21−H21•••N12	2 + *x*, −1 + *y*, z	3.3182 (8)	2.56	138
C23−H23•••N12	2 + *x*, −1 + *y*, z	3.3058 (8)	2.59	133
C17−H17C•••N14	1-x, 1-y, 1-z	3.5901 (9)	2.73	146
C4−H4B•••O4	−1 + *x*, y, z	3.6072 (10)	2.65	162
C17−H17B•••O2	1-x, -y, 1-z	3.4383 (9)	2.65	137
C4−H4A•••C24	−1 + *x*, 1 + *y*,+*z*	3.6322 (9)	2.87	134
C17−H17C•••C13	1-x, 1-y, 1-z	3.6823 (9)	2.71	171
C25•••C6	1 + *x*, y, z	3.3368 (9)		
C25•••C7	1 + *x*, y, z	3.3941 (9)		

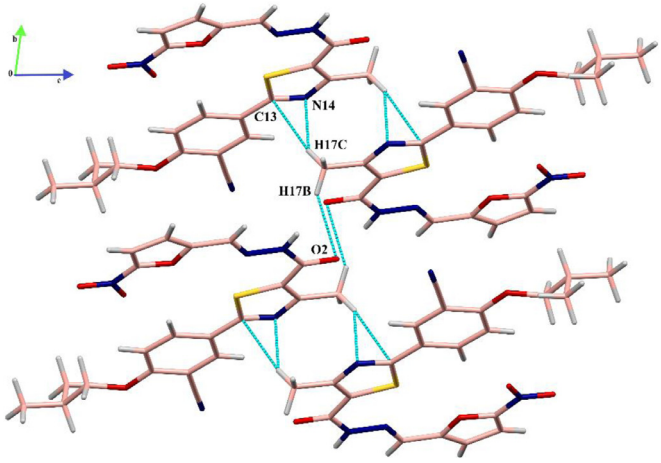


Fig. 3. Formation of molecular tetramer by means of C17−H17C•••N14/C13 and C17−H17B•••O2 hydrogen bonds.

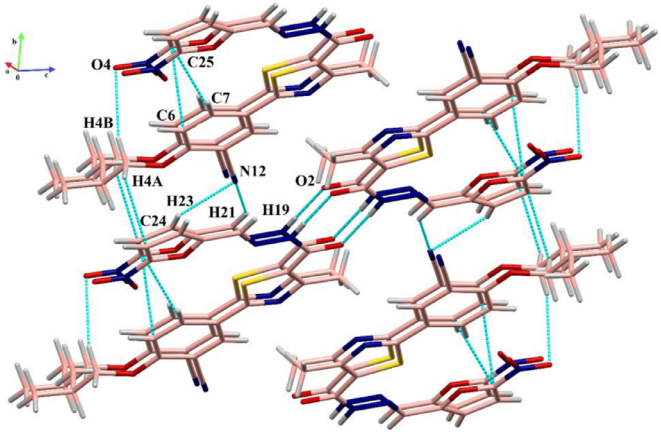


Fig. 4. Stabilizing interactions between the layers within the molecular stacks formed along *a* axis.

a axis are connected via C4−H4B•••O4 (Symmetry code: −1 + *x*, y, z) hydrogen bond and C25•••C6/C7 (Symmetry code: 1 + *x*, y, z) interactions. C21/23−H21/23•••N12 (Symmetry code: 2 + *x*, −1 + *y*, z) and C4−H4A•••C24 (Symmetry code: −1 + *x*, 1 + *y*, +*z*) hydrogen bonds also interlink the molecules within different layers. Weak Vander Waals interactions such as H•••H contacts make the molecular tetramer propagate along the *c* axis.

The relative contributions of different interactions in the crystal packing were analyzed from 2D- Finger-print plots generated using CrystalExplorer 17.5 software. The finger-print plots of NP61i, depicting the de, di distances to the Hirshfield surface, are shown in Fig. 5. It is evident that C•••H, H•••H, O•••H, and N•••H contacts play significant roles in the crystal packing, which together account for almost 80% of the Hirshfield surface.

Table 4
Larvicidal properties of arylhydrazones (5a-i) and (5j-l) at 4 µg/mL against *Anopheles arabiensis*.

Comp. Code	24 h	48 h
5a [A]	0.91 ± 0.03	0.92 ± 0.03
5b [BC]	0.49 ± 0.05	0.51 ± 0.05
5c [BC]	0.47 ± 0.05	0.51 ± 0.05
5d [D]	0.66 ± 0.05	0.70 ± 0.05
5e [D]	0.69 ± 0.05	0.73 ± 0.05
5f [BE]	0.56 ± 0.05	0.59 ± 0.05
5 g [AF]	0.84 ± 0.04	0.91 ± 0.03
5 h [C]	0.44 ± 0.05	0.48 ± 0.05
5i [ED]	0.61 ± 0.05	0.66 ± 0.05
5j [BE]	0.54 ± 0.05	0.59 ± 0.05
5k [D]	0.69 ± 0.05	0.73 ± 0.05
5l [F]	0.80 ± 0.04	0.83 ± 0.04
Acetone [G]	0.00 ± 0.00	0.04 ± 0.02
Temephos [H]	0.99 ± 0.01	1.00 ± 0.00

[A-H]Mean mortality of treatments not sharing a capital letter differs significantly ($p > 0.05$). Compounds exerting mortalities closer to the positive control are in bold.

3.3. Pharmacology

3.3.1. Larvicidal activity

Larval mortality resulting from exposure to the treatments is summarized in Table 4. There were significant effects of compounds ($F_{13,69} = 21.08$; $p < 0.0001$) and exposure time ($F_{1, 69} = 4.98$, $p = 0.03$). Overall the larval mortality was increased by 7% from 20 to 48 h of exposure. Larval mortality was highest for the positive control Temephos (99% after 48 h), followed by compounds (**5a**) (92%) and (**5 g**) (91%) as shown in (Table 4). Compounds (**5b**), (**5c**) and (**5 h**) were considered to have a low effect because they resulted in larval mortality ≤55% after 48 h of exposure; nevertheless, mortality was always significantly higher than the negative control. The remaining compounds had moderate larvicidal activity, with mortality ranging from approximately 60 to 84%. Compounds (**5a**) and (**5 g**), which showed the highest mortality, belonged to the hydrazone of (*E*)−2-(3-cyano-4-isobutoxyphenyl)-*N*'-(substituted-phenoxybenzylidene)−4-methylthiazole-5-carbohydrazide. However, compounds of this series also exhibited the lowest mortalities (e.g., compounds **5b, 5c**and **5 h**).On the other hand, compounds (**5k**) and (**5l**), both hydrazones of (*E*)−2-(3-cyano-4-isobutoxyphenyl)−4-methyl-*N*'-((5-(substituted-furan-2-yl)methylene)thiazole-5-carbohydrazide, resulted in mortalities higher than 71% (but compound **(5j)** showed a relatively low larvicidal activity, averaging 57% mortality).

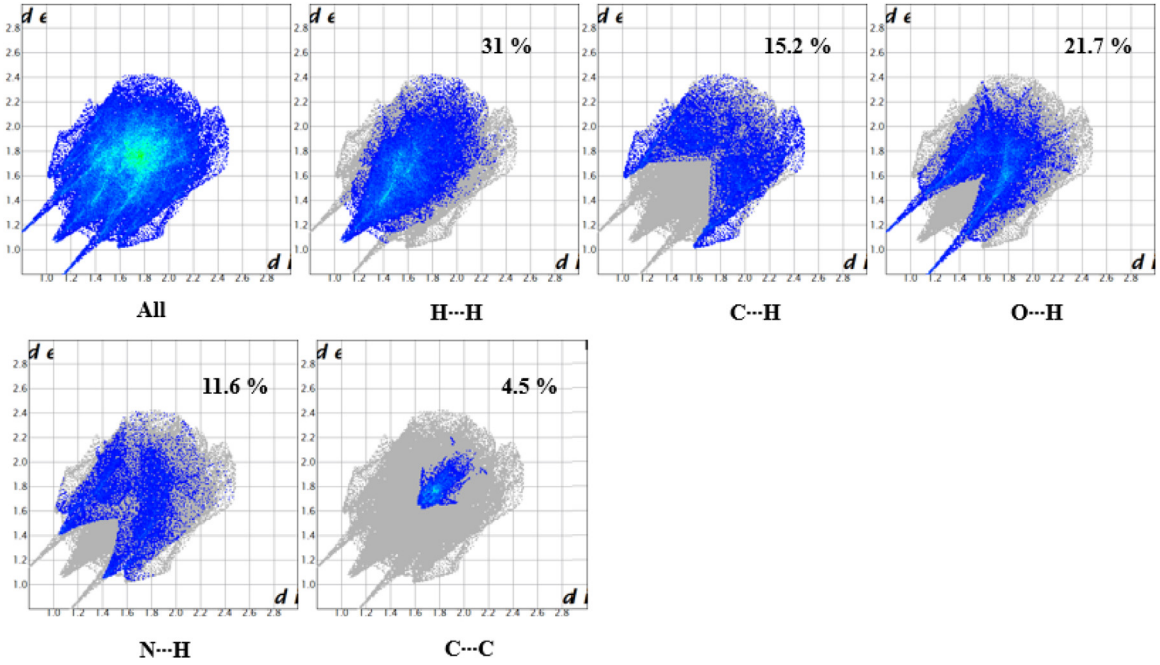


Fig. 5. 2D Finger-print plot of the compound (5l) decomposed into different interactions.

4. Conclusion

A series of hydrazones(**5a-l**) were obtained using a parent compound 2- [3-*cyano*-4-(2-*methylpropoxy*)*phenyl*]−4-methyl-1,3-thiazole-5-carbohydrazide (**4**). Two of the target compounds (**5a)** and (**5 g)** from the series exhibited promising larvicidal activity against *Anopheles arabiensis*. Among the series the compounds (**5a**) and (**5 g**) are known to have fluorine and chlorine respectively on the phenyl ring. Literature reveals that the substitution of hydrogen atoms by halogen atoms is the one of the possible routes to get promising pharmacological properties [61]. Moreover, halogen atoms in several heterocyclic compounds can act either as polar hydrogen atoms or a hydroxy mimicking moiety [62]. Thus the high result is attributed to the presence of fluorine and chlorine atoms on the phenyl ring of the compounds (**5a**) & (**5 g**). The presence of fluorine in the compound renders the unique properties such as, increased lipophilicity, resemblance of hydrogen's steric requirement, high electronegativity and stronger C-F bond which could help in building highly biological active molecules [63-64]. Further, larivicidal activity study of N- (benzylidene)−3-cyclohexylpropionic acid hydrazide derivatives [13], highlights the good activity of one of the compounds, owing to the presence of fluorine substituent as an electron withdrawing substituent on benzene ring. Hence, with all these literature support it can be concluded that the highest activity of the compound (**5a**) is due to the presence of fluorine atom in comparison with the compound (**5 g**) that bears chlorine atom on the phenyl ring. Title compounds (**5d**), (**5e**), **(5k)** and (**5l)** exhibited moderate activity in the range of 70–83% larvicidal activity when compared to the positive control Temephos at 99%. Remaining compounds (**5b**), (**5c**), (**5f**), (**5 h**), (**5i)** and (**5j)** exhibited low activity compared to a positive standard compound. The crystal structure of the compound (**5l)** is a cooperative interplay among strong N–H…O H-bonds, including weak C–H…O, C–H…N, C–H…π and π…π intermolecular interactions in molecular crystals.

Author credit statement

Pandikatte Nefisath

Design, synthesis, purification and writing the draft manuscript for publication.

Jagadeesh Prasad D

Overall mentoring, monitoring the chemical synthesis and supervision of manuscript correction, Co-ordination with co-authors

Haripriya B

Development of single crystal for X-ray studies, data collection, and refinement. Preparation of figures and tables, and writing crystallography results and discussion.

Deepak Chopra,

Monitoring the development of single crystal for X-ray studies, data collection, writing crystallography results and discussion. Hirshfield surface, 2D Finger-print plot discussion. Proofreading of the manuscript for final communication.

Katharigatta N. Venugopala conducting experiment on larvae of mosquito

Pran Kishore Deb larvicidal results, writing and reviewing of the manuscript for publication.

Raquel M. Gleiser

Preparation of table of content, editing the manuscript

Viresh Mohanlall

Mentoring & monitoring the Screening of the synthesized compounds for larvicidal activity.

RajendraMaharaj

Overall discussion & supervision of larvicidal results and writing the activity in the manuscript.

Screening of the title compounds for larvicidal activity, preparation, and proofreading of the manuscript.

Shashiprabha S characterization of the synthesized compounds, using FT-IR, ^{1}H NMR,^{13}C NMR and Mass spectral studies. Supervising the manuscript writing.

Vishwanatha Poojary

Analyzing the spectra and corrected the manuscript for publication.

Declaration of Competing Interest

Authors declare that there are no conflicts of interest

Acknowledgement

The authors are grateful to Sri Dharmasthala Manjunatheshwara College (Autonomous), Ujire, for providing laboratory facilities and encouragement. RM Gleiser is a CIC researcher of CONICET. DC thanks CIF, IISER Bhopal for research facilities and infrastructure.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130305.

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