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Synthesis, antileishmanial and cytotoxicity activities of fused and nonfused tetrahydroquinoline derivatives

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Abstract Developing novel antileishmanial, and cytotoxic drugs has been a significant area in modern pharmaceutical research. A series of novel triazolo[4,3-a]quinoline, triazino[4,3-a]quinoline, thiadiazepino[5,6-b]quinoline and pyrazolquinoline have been synthesized from the reaction of 2-hydrazinyltetrahydroquinoline-3-carbonitrile with formamide, formic acid, ethyl chloroacetate, carbon disulphide in an alcoholic solution of potassium hydroxide acetyl acetone and/or ethyl cyanoacetate, respectively. These compounds were evaluated for their in vitro studies against *L. major* leishmanial. The brine shrimp bioassay was also conducted to study their in vitro cytotoxic properties which displayed potent cytotoxic activity against Vincristine. The newly synthesized compounds were all characterized through IR, ^{1}H-NMR, and MS.

Keywords Tetrahydroquinolines · Triazolo[4,3-a]quinoline · Triazino[4,3-a]quinoline · Thiadiazepino[5,6-b]quinoline · Antileishmanial · Cytotoxicity

Introduction

Tetrahydroquinolines are one of the important structural subunits of various naturally occurring compounds and numerous recent reports have proved that compounds containing the tetrahydroquinoline moiety elicit potent biological responses leading to anti-inflammatory [1], antinephritic [2], treatment of Alzheimer's disease [3], antitumor [4, 5] and antiallergenic [6] activities. In addition, many tetrahydroquinoline derivatives appeared as anti-HIV [7, 8], antimalarial [9, 10] cholesteryl

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ester transfer protein inhibitors [11], anti-diabetic [12, 13] and antioxidant [14] agents. In recent years, the 5,6,7,8-tetrahydroquinolines have gained significant attention due to their remarkable biological applications as tyrosine kinase inhibitors, anticancer candidates [15] and cytotoxic activity against human colon carcinoma HT29, hepatocellular carcinoma HepG2 and Caucasian breast adenocarcinoma MCF7 cell lines [16].

In view of these points and related with our programme objectives of synthesis of fused heterocyclic compounds and their biological evaluation, [17–23] the authors' target, herein, it was thought worthwhile to study the synthesis of new heterocyclic systems fused with the tetrahydroquinoline ring system in a single molecular framework with the hope of getting agents of synergistic anticancer activity, lower toxicity towards the normal cells, and antileishmanial activity.

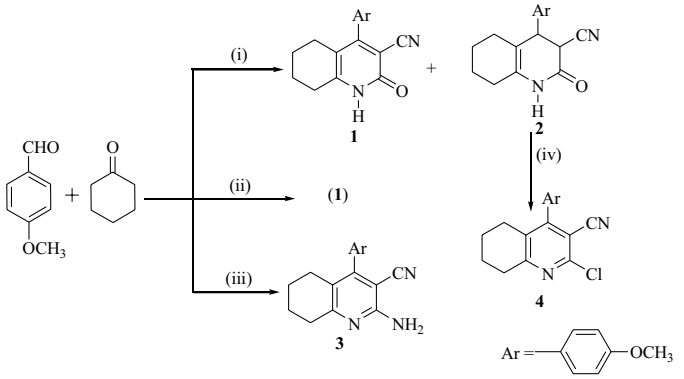
Result and discussion

Chemistry

A facile one-pot four-components reaction was utilized to construct a mixture of 4-(4-methoxyphenyl)-2-oxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carbonitrile **(1)** and 4-(4-methoxyphenyl)-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile **(2)**, via reaction of cyclohexanone, 4-methoxybenzaldehyde, ethyl cyanoacetate and ammonium acetate in ethanol. Compound **1** has been confirmed via the isolation of the same octahydroquinoline-3-carbonitrile **1** by the reaction of cyclohexanone, 4-methoxybenzaldehyde, cyanoacetamide and ammonium acetate in ethanol under reflux. It has been reported [24] that the reaction of cyclohexanone with the α,β-unsaturated nitrile derivative in the presence of ammonium acetate in ethanol gave the same products. Reaction of cyclohexanone, 4-methoxybenzaldehyde, malononitrile and ammonium acetate in ethanol under reflux gave enaminonitrile **3**. Chlorination of compound **2** with a mixture of phosphorous oxychloride and phosphorous pentachloride gave the corresponding 2-chlorotetrahydroquinoline-3-carbonitrile **4** (cf. Scheme 1).

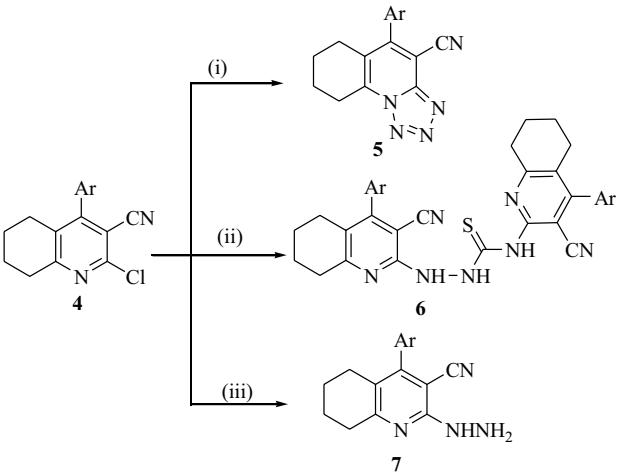
The reactivity of 2-chlorotetrahydroquinoline-3-carbonitrile **4** towards some nucleophilic reagents such as sodium azide, thiosemicarbazide and hydrazine hydrate in boiling ethanol has been investigated to give tetrahydrotetrazolo[1,5-a] quinoline **5**, bis compound **6** and 2-hydrazinyl-tetrahydroquinoline-3-carbonitrile **7**, respectively (cf. Scheme 2). The IR spectrum of compound **6** displayed absorption bands at 3349, 2221 and 1250 cm^{-1} attributed to ν_{NH}, $\nu_{C\equiv N}$ and $\nu_{C=S}$ respectively; its ^{1}H-NMR spectrum displays two singlet signals at 8.98 and 4.45 equivalent to a three NH group. The IR spectrum of **7** displayed absorption bands at 3420, 3350 cm^{-1} due to asymmetry and symmetry of the NH_2 group.

Compound **7** has been used in the synthesis of many novel biologically interesting fused and nonfused heterocyclic ring systems. Consequently, 2-hydrazinoquinoline **7** when heated with formamide, and/or formic acid afforded triazolo[4,3-a] quinoline derivatives **8** and **9**, respectively. Triazino[4,3-a]quinoline **10** has been synthesized by reacting 2-hydrazinoquinoline **7** with ethyl chloroacetate in pyridine



(i) $CNCH_2COOEt$, $AcONH_4$, EtOH; (ii) $CNCH_2CONH_2$, $AcONH_4$, EtOH; (iii) $CH_2(CN)_2$, $AcONH_4$, EtOH; (iv) $POCl_3$,PCl_5

Scheme 1 Synthesis of quinoline derivatives



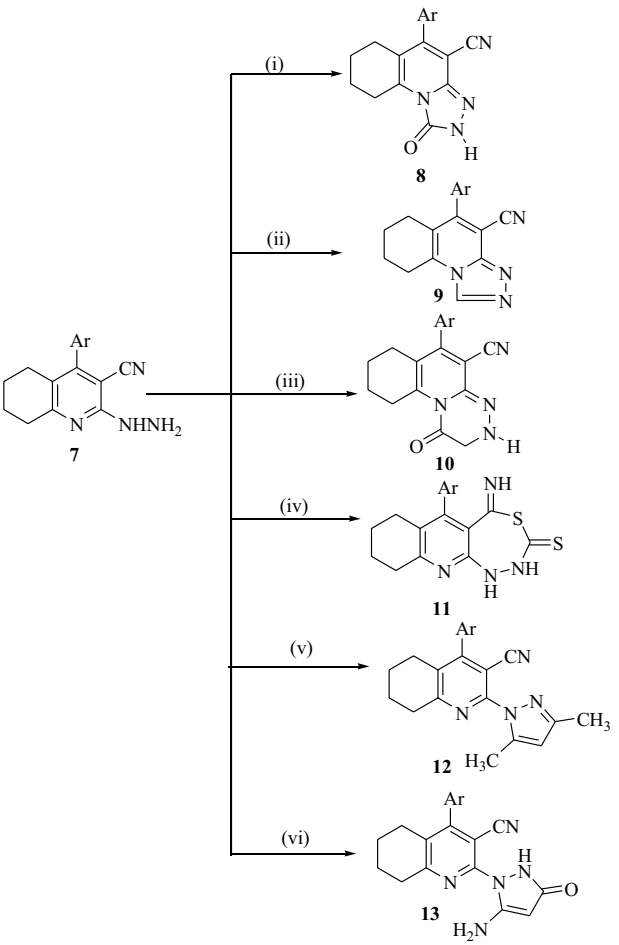
(i) NaN_3,DMF/reflux; (ii) $NH_2NHCSNH_2$, EtOH, reflux; (iii) $NH_2NH_2.H_2O$, EtOH, reflux

Scheme 2 Reactions of 2-chlorotetrahydroquinoline-3-carbonitrile **4** with different nitrogen nucleophiles

via a S_N^2 reaction mechanism on the electron deficient CH_2 group present between the carbonyl group and chlorine atom of the ethyl chloroacetate followed by cyclization through attack of the imino group of the pyridone nucleus on the carbonyl of ester group via the tetrahedral mechanism. However, reaction of 2-hydrazinoquinoline **7** with carbon disulphide in an alcoholic solution of potassium hydroxide gave thiadiazepino[5,6-b]quinoline derivative **11**. According to our speculation, the latter compound **11** was synthesized through nucleophilic attack of the amino group of the 2-hydrazinoquinoline **7** on the electron deficient C-atom of carbon disulfide and the subsequent 1,3-proton shift and cyclization via attachment of the thiol functionality

on the cyano group through a S_N^i reaction mechanism. On the other hand, pyrazolquinoline derivatives **12** and **13** have been obtained via reaction of 2-hydrazinoquinoline **7** with acetyl acetone and/or ethyl cyanoacetate in ethanol, respectively (cf. Scheme 3).

The reactivity of the starting 2-hydrazinoquinoline **7** towards acetic anhydride under all sets of conditions was investigated. The starting material **7** was heated at refluxing temperature with acetic anhydride to afford *N*-acetyl-*N*′-[3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl] acetohydrazide **(14)**. On the other hand, fusing of 2-hydrazinoquinoline **7** with acetic anhydride gave an acetylated product then hydrolysis of a cyano group into carboxylic acid



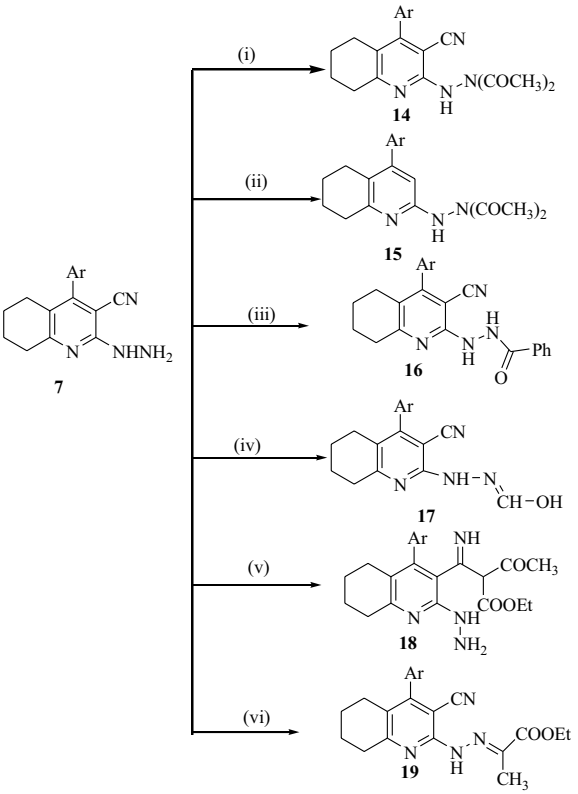
(i) $HCONH_2$; (ii) HCOOH; (iii)$ClCH_2COOEt$, pyridine ; (iv)CS_2, alc. KOH; (v) $CH_3COCH_2COCH_3$, EtOH; (vi) $CNCH_2COOEt$, EtOH

Scheme 3 Synthesis of fused and nonfused tetrahydroquinoline derivatives

followed by decarboxylation to afford *N*-acetyl-*N*′-[4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2-yl]acetohydrazide **(15)**.

Furthermore, when 2-hydrazinoquinoline **7** was treated with benzoyl chloride and/or triethyl orthoformate, the isolated products have been identified as quinolin-2-ylbenzohydrazide **16** and tetrahydroquinoline-3-carbonitrile derivatives **17,** respectively. It seems that compound **17** was formed as a result of nucleophilic substitution on the electronically deficient carbon of triethyl orthoformate followed by demethylation (cf. Scheme 4).

We studied the reaction of ethyl acetoacetate with 2-hydrazinoquinoline **7** in ethanol in the presence of a basic catalyst, namely, piperidine and/or in absence of it. In the first case, the isolated product has been identified as ethyl 2-(imino(4-(4-methoxyphenyl)-2-hydrazinyl-5,6,7,8-tetrahydroquinolin-3-yl)methyl)-3-oxobutanoate (**18**). According to our speculation, the presence of piperidine lead to formation of the carbanion from the electronically deficient methylene group flanked between the two carbonyl groups of ketone and ester of the reagent. The generating



(i) Ac_2O/ reflux; (ii) Ac_2O / fusion; (iii)PhCOCl, EtOH ; (iv)$CH(OEt)_3$; (v) $EtOCOCH_2COCH_3$, EtOH, piperidine; (vi) $EtOCOCH_2COCH_3$, EtOH

Scheme 4 Reactions of 2-hydrazinyl-tetrahydroquinoline-3-carbonitrile **7** with different electrophiles

carbanion subsequently attacked the cyano group to form the final product. When the same reaction was conducted in the absence of piperidine, the *N*-nucleophile amino group attacked the carbonyl carbon of the ketonic group as an electrophilic center to afford ethyl 2-(2-(3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl)hydrazono)propanoate (**19**).

Biological activity

Antileishmanial activity

In the present studies on heterocyclic compounds against *L. major* leishmania, it is evident that from (Table 1) a series of heterocyclic compounds showed tremendous activity toward *L. major* leishmania. Compound **5**, **10**, **13** and **19** have shown significant activity against *L. major* with IC_{50} values of 0.58 ± 0.08 and 0.59 ± 0.07 µg/ml, respectively, compared to Amphotericin B (standard drug) IC_{50} value (0.56 ± 0.20 µg/ml). On the other hand, further compounds **4**, **6**–**8** and **11**–**17** showed a good activity against *L. major* with IC_{50} values of 0.60 ± 0.27

Table 1 % Inhibition of compounds **1**–**19** against *L. major* leishmania

Compounds numbers	*L. major* leishmania, (µg/ml ± SD)
1	0.80 ± 0.09
2	0.82 ± 0.01
3	0.77 ± 0.09
4	0.69 ± 0.09
5	0.59 ± 0.09
6	0.63 ± 0.09
7	0.62 ± 0.09
8	0.67 ± 0.09
9	0.72 ± 0.09
10	0.59 ± 0.09
11	0.62 ± 0.09
12	0.65 ± 0.09
13	0.64 ± 0.09
14	0.68 ± 0.09
15	0.65 ± 0.09
16	0.60 ± 0.09
17	0.61 ± 0.09
18	0.58 ± 0.09
19	0.57 ± 0.09
Standard drug IC_{50} (µg/ml ± SD) Amphotericin B	0.56 ± 0.20

% Inhibition activity: 0.99 ± 0.00 = non-significant, 0.95–0.80 = low, 0.79–0.70 = moderate, 0.69–0.60 = good, < 0.59–0.56 = significant

and 0.69 ± 0.03 µg/ml, respectively. The rest of the compounds have shown moderate to low activity against *L.major* parasite with IC_{50} values for compounds **3** (0.77 ± 0.09 µg/ml) and **9** (0.72 ± 0.09 µg/ml). *L. major* leishmania showed resistance toward compounds **1** and **2.**

Cytotoxicity activity by brine-shrimp lethality assay

The crown gall is a neoplastic disease of plants which is initiated by the Gram-positive bacteria *Agrobacterium tumefaciens*. Since the mechanism of tumor induction resembles that in animals, this test has been used previously to prescreen antitumor activity of natural and synthetic compounds. According to the data shown in Table 2, most of the test compounds of this series **1–19** showed significant levels of tumor inhibition. Compound **19** showed 100% tumor inhibition that is comparable to the standard drug Vincristine (100% tumor inhibition). Compound **4** showed 21.42%, compound **6** showed 29.33%, compound **7**, **8** showed 29.33%, compound **11** showed 24. 05%, compound **13** showed 21.42%, compound **14** showed 37.58%,

Table 2 Antitumor activity of compounds **1–19**

Compounds no.	Average number of tumors[a] ± SE	% Inhibition of tumors[b,c]
1	8.5 ± 0.01	16.53
2	7.1 ± 0.03	18.22
3	8.2 ± 0.07	16.42
4	6.7 ± 0.07	21.42
5	7.5 ± 0.07	18.53
6	5.3 ± 0.84	29.33
7	5.3 ± 0.84	29.33
8	5.1 ± 0.33	29.01
9	7.5 ± 0.12	18.47
10	6.9 ± 0.07	19.79
11	6.3 ± 0.55	24.05
12	7.2 ± 0.09	17.62
13	6.7 ± 0.07	21.42
14	5.5 ± 0.66	37.58
15	7.2 ± 0.02	18.40
16	8.7 ± 0.07	17.13
17	5.1 ± 0.38	29.89
18	6.4 ± 1.98	43.59
19	0.0 ± 0.0	100
Vincristine	0.0 ± 0.0	100
Vehicle control: DMSO	8.3 ± 0.931	

[a]Potato disc antitumor assay, concentration: 1000 µg/ml in DMSO

[b]More than 20% tumor inhibition is significant

[c]Data represents mean value of 15 replicates

compound **17** showed 29.89%, compound **18** showed 43.59%, and tumor inhibition that is comparable to the standard drug Vincristine (100% tumor inhibition).

Experimental

Melting points measurement was made on Gallenkamp melting point apparatus and is uncorrected. The IR spectra were noted in (KBr) potassium bromide disks on a Pye Unicam SP-3-300 IR spectrophotometer. The ^{1}H-NMR experiment was done at 300 and 400 MHz on a Varian Mercury VX-300 NMR spectrometer using TMS as the internal standard in deuterated chloroform or deuterated dimethylsulphide. Chemical shifts are quoted δ. The mass spectra were measured on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV. All spectral measurements were carried out at the Central Laboratory of Ain-Shams University and the Main Defense Chemical Laboratory, Egypt. Biological activity was carried out in the Department of Pharmacy, COMSATS Institute of Information Technology, and Abbottabad, Pakistan. All the newly synthesized compounds gave adequate elemental analyses. The purity of the newly synthesized compounds has been checked through TLC.

Synthesis

Method A

4-(4-Methoxyphenyl)-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (1) and 4-(4-methoxyphenyl)-2-1,2,3,4,5,6,7,8-octahydroquinoline-3-carbonitrile (2) A mixture of cyclohexanone (10 mmol, 0.98 ml), ethyl cyanoacetate (10 mmol, 1.14 ml), 4-methoxybenzaldehyde (10 mmol, 1.36 ml) and ammonium acetate (80 mmol, 6.16 g) in absolute ethanol (30 ml) was heated under reflux for 9 h. The resultant precipitate was subjected to filtration on heat, and recrystallized from dioxane to give octahydroquinolinone **2** as yellow crystals, mp 208–210 °C, (Lit. 212–214 °C) [24], yield 75%. The filtrate obtained was allowed to cool at room temperature, and the solid product was collected, dried and recrystallized from ethanol to give **1** as a pale yellow crystal, mp 287–289 °C, (Lit. 291–293 °C) [24], yield 25%.

Method B

4-(4-methoxyphenyl)-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (1) A mixture of cyclohexanone (10 mmol, 0.98 ml), cyanoacetamide (10 mmol, 0.8 g), 4-methoxybenzaldehyde (10 mmol, 1.36 ml) and ammonium acetate (80 mmol, 6.16 g) in absolute ethanol (30 ml) was heated at reflux for 7 h. The mixture left to cool at room temperature, and the solid product was collected, dried and recrystallized from ethanol to give **1** as a pale yellow crystal, mp 287–289 °C, yield 63%.

2-Amino-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (3) A mixture of cyclohexanone (10 mmol, 0.98 ml), malononitrile (10 mmol, 2.2 g), 4-methoxybenzaldehyde (10 mmol, 1.36 ml) and ammonium acetate (80 mmol, 6.16 g) in absolute ethanol (30 ml) was heated at reflux for 9 h, then left to cool at room temperature. The solid product was collected, dried and recrystallised from dioxane to give enaminonitrile 3 as brown crystals, mp 249–250 °C, yield 65% [25, 26].

2-Chloro-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4) A mixture of octahydroquinolinone **2** (5 mmol, 1.4 g), phosphorous pentachloride (5 mmol, 1.25 g) and phosphorous oxychloride (5 mmol, 3.5 ml) was refluxed in a water bath for 6 h., then allowed to cool and poured into ice–cold water. The separated material was collected by filtration, washed with water, dried and recrystallised from ethanol to give **4** pale brown crystals, mp 161–163 °C, (Lit. 170 °C) [27], yield 75%. FT-IR (KBr, cm^{-1}): disappearance of ν_{NH}, 3068 ν_{CH} aromatic, 2933 ν_{CH} aliphatic, 2227 $\nu_{C\equiv N}$, 1660 $\nu_{C=N}$, 1608 $\nu_{C=C}$. ^{1}HNMR (300 MHz, DMSO-d_6): 7.35–7.08 (m, 4H, Ar–H), 3.84 (s, 3H, OCH_3) 2.95–1.65 (m, 8H, cyclohexene moiety). *Anal.* Calcd. for $C_{17}H_{15}ClN_2O$ (298.77): C, 68.34; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 68.12; H, 5.14; Cl, 11.76; N, 9.25.

5-(4-Methoxyphenyl)-6,7,8,9-tetrahydrotetrazolo[1,5-a]quinoline-4-carbonitrile (5) To a solution of tetrahydroquinoline **4** (5 mmol, 1.5 g) in DMF (20 ml), sodium azide (5 mmol 0.3 g) was added then refluxed for 4 h, left to cool, and poured into ice–cold water. The separated material was collected by filtration, washed with water, dried and recrystallized from methanol to give tetrazolo[1,5-a]quinoline **5** as pale orange crystals, mp 215–217 °C, yield 47% FT-IR (KBr,cm^{-1}): 3069 ν_{CH} aromatic, 2933 ν_{CH} aliphatic 2209 $\nu_{C\equiv N}$, 1668 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO): 7.34–7.07 (m, 4H, Ar–H), 3.89 (s, 3H, OCH_3), 2.93–1.68 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 305 (M^+, 20.11), 297 (19.22), 206 (100.00), 194 (17.57), 132 (18.97), 119 (10.56), 68 (4.62). *Anal.* Calcd. for $C_{17}H_{15}N_5O$ (305.33): C, 66.87; H, 4.95; N, 22.94. Found: C, 66.67; H, 4.78; N, 22.82.

1,4-Bis(3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl)thiosemicarbazide (6) A mixture of tetrahydroquinoline **4** (5 mmol, 1.5 g) and thiosemicarbazide (5 mmol, 0.5 g) in ethanol (20 ml) was heated and refluxed for 10 h, then the mixture was left to cool to room temperature. The solid product was collected, dried and recrystallised from dioxane to give tetrahydroquinoline derivative **6** as pale brown crystals, mp 231–233 °C, yield 65%. FT-IR (KBr, cm^{-1}): 3349 ν_{NH}, 3069 ν_{CH} aromatic, 2933 ν_{CH} aliphatic, 2221 $\nu_{C\equiv N}$, 1607 $\nu_{C=N}$, 1250 $\nu_{C=S}$. ^{1}HNMR (400 MHz, DMSO-d_6): 8.98 (s, 2H, 2NH, D_2O exchangeable), 7.50–7.15 (m, 8H, Ar–H), 4.45 (s, 1H, NH, D_2O exchangeable), 3.80 (s, 6H, OCH_3), 2.92–1.02 (m, 16H, cyclohexane ring protons). MS (*m/z* (%)): 556 (M-2OCH_3 + 2H]$^+$, 0.87), 533 (4.55), 438 (22.27), 437 (23.49), 421 (9.90), 386 (3.86), 347 (7.97), 270 (12.70), 246 (13.16), 244 (12.24), 220 (100.00), 193 (25.65), 176 (47.95). *Anal.* Calcd. for

$C_{35}H_{33}N_7O_2S$ (615.75): C, 68.27; H, 5.40; N, 15.92; S, 5.21. Found: C, 68.14; H, 5.32; N, 15.76; S, 5.15.

2-Hydrazinyl-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (7) A mixture of tetrahydroquinoline **4** (5 mmol, 1.5 g) and hydrazine hydrate (10 mmol, 0.5 ml) in ethanol (20 ml) was heated under reflux for 12 h, then the mixture was allowed to cool. The solid residue was collected, dried and recrystallised from dioxane to give 2-hydrazinoquinoline derivative **7** as pale orange crystals, mp 275–277 °C, yield 54%. FT-IR (KBr, cm^{-1}): 3420, 3350 ν_{NH}, ν_{NH2}, 3070 and 3005 ν_{CH} aromatic, 2934 ν_{CH} aliphatic, 2226 $\nu_{C\equiv N}$,1647 $\nu_{C=N}$. ^{1}HNMR (300 MHz, $CDCl_3$): 11.70 (s, 1H, NH, D_2O exchangeable), 7.27- 7.07 (m, 4H, Ar–H), 4.02 (s, 2H, NH_2, D_2O exchangeable), 3.56 (s, 3H, OCH_3), 2.93-1.68 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 294 (M^+, 6.71), 263 (1.44), 187 (3.94), 173 (16.84), 132 (11.7), 91 (100.00), 90 (4.56). *Anal.* Calcd. for $C_{17}H_{18}N_4O$ (294.35): C, 69.37; H, 6.16; N, 19.03. Found: C, 69.21; H, 6.01; N, 18.94.

5-(4-Methoxyphenyl)-1-oxo-1,2,6,7,8,9-hexahydro[1,2,4]triazolo[4,3-a]quinoline-4-carbonitrile (8) A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in formamide was heated under reflux for 6 h, then left to cool, and transferred into ice–cold water. The crude solid residue was collected by filtration, washed, dried and recrystallised from ethanol to give triazolo[4,3-a]quinoline derivative **8** as pale green crystals, mp 229–250 °C, yield 81%. FT-IR (KBr, cm^{-1}): 3385 ν_{NH}, 3080 ν_{CH} aromatic, 2935ν_{CH} aliphatic, 2219 $\nu_{C\equiv N}$, 1688$\nu_{C=O}$, 1654 $\nu_{C=N}$, 1607 $\nu_{C=C}$. ^{1}HNMR (300 MHz, DMSO-d_6): 12.29 (s, 1H, NH, D_2O exchangeable), 7.36-7.04 (m, 4H, Ar–H), 3.81 (s, 3H, OCH_3), 2.72-1.55 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 320 (M^+, 4.63), 294 (6.45), 280 (100.00), 199 (1.68), 138 (11.30), 133 (84.31), 83 (5.39), 56 (6.56). *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$ (320.35): C, 67.49; H, 5.03; N, 17.49. Found: C, 67.35; H, 5.12; N, 17.32.

5-(4-Methoxyphenyl)-6,7,8,9-tetrahydro[1,2,4]triazolo[4,3-a]quinoline-4-carbonitrile (9) A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in formic acid was heated under reflux for 8 h, allowed to cool and transferred into ice–cold water. The separated material was collected by filtration, washed, dried and recrystallised from ethanol to give triazolo[4,3-a]quinoline derivative **9** as pale brown crystals, mp 220–222 °C, yield 67%. FT-IR (KBr, cm^{-1}): 3011 ν_{CH} aromatic, 2936 ν_{CH} aliphatic, 2220 $\nu_{C\equiv N}$, 1648 $\nu_{C=N}$, 1606 $\nu_{C=C}$. ^{1}HNMR (400 MHz, DMSO-d_6): 8.25 (s, 1H, C–H olefnic), 7.67–6.82 (m, 4H, Ar–H), 3.90 (s, 3H, OCH_3), 2.81–1.55 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 304 (M^+, 4.66), 272 (2.34), 252 (4.35), 199 (5.05), 71 (100.00), 57 (81.08). *Anal.* Calcd. for $C_{18}H_{16}N_4O$ (304.35): C, 71.04; H, 5.30; N, 18.41. Found: C, 71.12; H, 5.25; N, 18.22.

6-(4-Methoxyphenyl)-1-oxo-2,3,7,8,9,10-hexahydro-1H-[1,2,4]triazino[4,3-a]quinoline-5-carbonitrile (10) A mixture of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) and ethyl chloroacetate (5 mmol, 0.6 ml) in pyridine (25 ml) was heated under reflux for 18 h. The reaction mixture is allowed to cool then neutralized with dilute

hydrochloric acid, the product was collected by filtration, washed with water, dried and recrystallised from ethanol to give triazino[4,3-a]quinoline **10** as pale brown crystals, mp 173 dec., yield 76%. FT-IR (KBr, cm^{-1}): 3433, 3377 ν_{NH}, 3069 ν_{CH} aromatic, 2999 ν_{CH} aliphatic, 2216 $\nu_{C\equiv N}$, 1722 $\nu_{C=O}$, 1668 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 11.73 (s, 1H, NH, D_2O exchangeable), 7.34–7.06 (m, 4H, Ar–H), 3.88 (s, 2H, $-COCH_2$), 3.82 (s, 3H, OCH_3), 2.9–1.65 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 338 (M + 4, 7.06), 334 (7.45), 276 (18.28), 226 (18.93), 199 (12.25), 170 (10.67), 135 (20.25), 126 (100.00), 97 (9.78), 58 (11.34). *Anal.* Calcd. for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.01; H, 5.23; N, 16.54.

5-Imino-6-(4-methoxyphenyl)-1,2,7,8,9,10-hexahydro[1,3,4]thiadiazepino[5,6-b] quinoline-3(5H)-thione (11) A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in potassium hydroxide (5 mmol, 0.28 g) absolute ethanol (20 ml), and carbon disulfide (15 mmol, 1.14 ml) were mixed. The mixture was heated in a water bath for 10 h, then left to cool, poured into water, and neutralized with dilute hydrochloric acid. Separated solid was collected by filtration, washed, dried and recrystallised from methanol to give thiadiazepino[5,6-b]quinoline derivative **11** as pale brown crystals, mp over 300 °C, yield 70%. FT-IR (KBr, cm^{-1}): 3306, 3192 ν_{NH}, 3029 ν_{CH} aromatic, 2937 ν_{CH} aliphatic, disappearance of $\nu_{C\equiv N}$, 1615 $\nu_{C=N}$, 1245 $\nu_{C=S}$. ^{1}HNMR (300 MHz, DMSO-d_6): 11.73 (s, 1H, NH, D_2O exchangeable), 7.24- 7.07 (m, 4H, Ar–H), 4.05 (s, 1H, NH, D_2O exchangeable), 3.82 (s, 3H, OCH_3), 3.52 (s, 1H, NH, D_2O exchangeable), 2.92-1.65 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 370 (M^+, 0.91), 314 (12.05), 209 (2.93), 119 (100.00), 107 (36.61), 56 (5.08), 52 (17.56). *Anal.* Calcd. for $C_{18}H_{18}N_4OS_2$ (370.49): C, 58.35; H, 4.90; N, 15.12; S, 17.31. Found: C, 58.22; H, 4.74; N, 15.01; S, 17.26.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (12) A mixture of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) and acetylacetone (5 mmol, 0.5 ml) in absolute ethanol (25 ml) was heated at reflux for 17 h, then left to cool. The solid product was collected, dried and recrystallised from benzene to give tetrahydroquinoline derivative **12** as pale yellow crystals, mp over 300 °C, yield 55%. FT-IR (KBr, cm^{-1}): 3035 ν_{CH} aromatic, 2932 ν_{CH} aliphatic, 2217 $\nu_{C\equiv N}$, 1670 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 7.61- 7.06 (m, 5H, Ar–H), 3.84 (s, 3H, OCH_3), 2.98-2.02 (m, 8H, cyclohexane ring protons), 1.22 (s, 6H, $2CH_3$). MS (*m/z* (%)): 360 (M + 2, 4.16), 258 (100.00), 332 (2.22), 302 (2.13), 263 (4.78), 251 (18.07), 226 (2.27), 157 (8.15), 95 (38.08). *Anal.* Calcd. for $C_{22}H_{22}N_4O$ (358.44): C, 73.72; H, 6.19; N, 15.63. Found: C, 73.56; H, 6.05; N, 15.58.

2-(5-Amino-3-oxo-2,3-dihydropyrazol-1-yl)-4-(4-methoxy-phenyl)-5,6,7,8-tetrahydro-quinoline-3-carbonitrile (13) A mixture of 2-hydrazinoquinoline 7 (5 mmol, 1.4 g) and ethyl cyanoacetate (5 mmol, 0.6 ml) in ethanol (25 ml) was heated under reflux for 13 h, then left to cool. The precipitated solid residue was collected, dried and recrystallised from dioxane/water to give 13 as brown crystals, mp 173–175 °C, yield 63%. FT-IR (KBr, cm^{-1}): 3300, 3194, 3143 ν_{NH2}, ν_{NH},

3031 ν_{CH} aromatic, 2934 ν_{CH} aliphatic, 2221 $\nu_{C\equiv N}$, 1642 $\nu_{C=O}$, 1605 $\nu_{C=N}$. ^{1}HNMR (300 MHz, DMSO-d_6): 11.73 (s, 1H, NH, D_2O exchangeable), 7.45- 7.01 (m, 4H, Ar–H), 4.54 (s, 1H, pyrazolone-H), 3.84 (s, 3H, OCH_3), 2.11 (s, 2H, NH_2, D_2O exchangeable), 2.92-1.65 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 361 (M^+, 6.43), 294 (86.67), 280 (30.37), 263 (7.86), 98 (16.08), 43 (100.00). *Anal.* Calcd. for $C_{20}H_{19}N_5O_2$ (361.4): C, 66.47; H, 5.30; N, 19.38. Found: C, 66.25; H, 5.16; N, 19.23.

***N*-Acetyl-*N′*-[3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl] acetohydrazide (14)** A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in acetic anhydride (10 ml) was refluxed for 7 h, then transferred into ice/cold water along with stirring. The crude solid residue that deposited was collected by filtration, washed, dried and recrystallised from methanol to give acetohydrazide derivative **14** as pale brown crystals, mp 230–232 °C, and yield 72%. FT-IR (KBr, cm^{-1}): 3199 ν_{NH}, 3070 ν_{CH} aromatic, 2935 ν_{CH} aliphatic, 2226 $\nu_{C\equiv N}$, 1729 $\nu_{C=O}$ imide, 1607 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 9.83 (s, 1H, NH, D_2O exchangeable), 7.37–6.97 (m, 4H, Ar–H), 3.85 (s, 3H, OCH_3), 3.06 (s, 6H, $(COCH_3)_2$), 2.9-1.77 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 380 (M + 2, 1.74), 334 (5.07), 294 (100.00), 284 (1.66), 271 (3.07), 246 (12.76), 199 (8.79), 181 (4.16), 179 (7.15), 158 (2.70). *Anal.* Calcd. for $C_{21}H_{22}N_4O_3$ (378.42): C, 66.65; H, 5.86; N, 14.81. Found: C, 66.54; H, 5.72; N, 14.69.

***N*-Acetyl-*N′*-[4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl]aceto-hydrazide (15)** A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in acetic anhydride (5 ml) was fused for 7 h at 200 °C, then transferred into ice/cold water along with stirring. The crude solid residue that deposited was collected by filtration, washed, dried and recrystallised from dioxine/water to give acetohydrazide derivative 15 as pale brown crystals, mp 160–162 °C, and yield 72%. FT-IR (KBr, cm^{-1}): 3175 ν_{NH}, 3011 ν_{CH} aromatic, 2937 ν_{CH} aliphatic, 1728 $\nu_{C=O}$ imide, 1610 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 11.80 (s, 1H, NH, D_2O exchangeable), 7.34–7.01 (m, 5H, Ar–H), 3.85 (s, 3H, OCH_3), 2.32 (s, 6H, $(COCH_3)_2$), 3.27–1.83 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 353 (M^+, 1.80), 322 (10.79), 294 (100.00), 246 (3.76), 215 (2.21), 156 (1.00), 115 (4.62), 102 (3.08). *Anal.* Calcd. for $C_{20}H_{23}N_3O_3$ (353.41): C, 67.97; H, 6.56; N, 11.89. Found: C, 67.85; H, 6.42; N, 11.75.

***N′*-(3-Cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinolin-2-yl)benzohydrazide (16)** A mixture of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) and benzoyl chloride (5 mmol, 0.7 ml) in absolute ethanol (25 ml) was heated at reflux for 5 h, then left to cool. The solid product was collected, dried and recrystallised from methanol to give benzohydrazide derivative **16** as pale orange crystals, mp 244–246 °C, and yield 75%. FT-IR (KBr, cm^{-1}): 3199 ν_{NH}, 3053 ν_{CH} aromatic, 2958 ν_{CH} aliphatic, 2218 $\nu_{C\equiv N}$, 1666 $\nu_{C=O}$, 1632 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 10.64 (s, 2H, 2NH, D_2O exchangeable), 7.91–7.48 (m, 9H, Ar–H), 3.54 (s, 3H, OCH_3), 2.9–1.77 (m, 8H, cyclohexane ring protons). MS (*m/z* (%)): 398 (M^+, 2.04), 291

(5.85), 278 (2.02), 120 (11.93), 108 (70.47), 101 (100.00), 76 (93.33). *Anal.* Calcd. for $C_{24}H_{22}N_4O_2$ (398.46): C, 72.34; H, 5.57; N, 14.06. Found: C, 72.15; H, 5.43; N, 14.18.

4-(4-Methoxyphenyl)-2-(2-hydroxymethylenehydrazinyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (17) A solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g), in triethyl orthoformate (10 ml) was refluxed for 19 h, and left to cool. The solid product was collected, dried and recrystallised from pet 80–100 to give quinolin-2-ylhydrazonoformate derivative **17** as pale red crystals, mp 193–195 °C, and yield 75%. FT-IR (KBr, cm^{-1}): 3454 ν_{OH}, 3301ν_{NH}, 3029 ν_{CH} aromatic, 2932 ν_{CH} aliphatic, 2211 $\nu_{C\equiv N}$, 1607 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 11.71 (s, 1H, NH, D_2O exchangeable), 7.46–7.03 (m, 5H, Ar–H & N = CH), 3.81 (s, 3H, OCH_3), 3.28 (s, 1H, OH, D_2O exchangeable), 2.90–1.61 (m, 8H, cyclohexane ring protons). MS (*m*/*z* (%)): 323 (M + 1, 1.21), 308 (8.98), 267 (30.86), 266 (13.67), 240 (15.44), 220 (30.53), 172 (11.19), 165 (14.89), 151 (11.64), 136 (16.89), 43 (100.00). *Anal.* Calcd. for $C_{18}H_{18}N_4O_2$ (322.36): C, 67.07; H, 5.63; N, 17.38. Found: C, 67.14; H, 5.50; N, 17.24.

Ethyl 2-(imino(4-(4-methoxyphenyl)-2-hydrazinyl-5,6,7,8-tetrahydroquinolin-3-yl)me-thyl)-3-oxobutanoate (18) A mixture of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) and ethyl acetoacetate (5 mmol, 0.7 ml), and two drops of piperidine in absolute ethanol (25 ml) was refluxed for 15 h, then allowed to cool. The resultant solid product was collected, dried and recrystallised from methanol to give 2-hydrazinoquinoline derivative **18** as pale red crystals, mp over 300 °C, and yield 65%. FT-IR (KBr, cm^{-1}): 3442, 3202 $\nu_{NH2,\ NH}$, 3027 ν_{CH} aromatic, 2959 ν_{CH} aliphatic, 1727 $\nu_{C=O}$ ester, 1700 $\nu_{C=O}$ ketone, 1605 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 12.94 (s, 1H, NH, D_2O exchangeable), 7.46–6.97 (m, 4H, Ar–H), 5.79 (s, 1H, $\underline{CH}COCH_3$), 4.60 (s, 2H, NH_2, D_2O exchangeable), 4.20 (s, 1H, NH, D_2O exchangeable), 3.86 (s, 3H, OCH_3), 3.79 (q, 2H, CH_2CH_3), 2.45 (s, 3H, $COCH_3$), 2.34-1.01 (m, 8H, cyclohexane ring protons), 0.81 (t, 3H, CH_2CH_3). MS (*m*/*z* (%)): 424 (M^+, 1.82), 368 (0.85), 317 (2.23), 265 (0.73), 164 (100.00), 157 (3.21), 107 (48.09). *Anal.* Calcd. for $C_{23}H_{28}N_4O_4$ (424.49): C, 65.08; H, 6.65; N, 13.20. Found: C, 65.23; H, 6.54; N, 13.08.

Ethyl 2-(2-(3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-yl) hydrazono)prop-anoate (19) To a solution of 2-hydrazinoquinoline **7** (5 mmol, 1.4 g) in absolute ethanol (25 ml), ethyl acetoacetate (5 mmol, 0.7 ml), was added, then reflux of the reaction mixture was done for 15 h, and left to cool. The solid product was collected, dried and recrystallised from methanol to give **19** as pale red crystals, mp over 300 °C, and yield 65%. FT-IR (KBr, cm^{-1}): 3194ν_{NH}, 3050 ν_{CH} aromatic, 2934 ν_{CH} aliphatic, 2214 $\nu_{C\equiv N}$, 1735 $\nu_{C=O}$ ester, 1658 $\nu_{C=N}$. ^{1}HNMR (400 MHz, DMSO-d_6): 7.37–6.99 (m, 4H, Ar–H), 4.20 (q, 2H, CH_2CH_3), 3.88 (s, 3H, OCH_3), 3.44 (s, 1H, NH, D_2O exchangeable), 2.82-1.57 (m, 8H, cyclohexane ring protons), 1.30 (t, 3H, CH_2CH_3), 0.84 (s, 3H, CH_3). MS (*m*/*z* (%)): 391 (M^+, 2.39), 335 (1.59), 251 (22.41), 223 (0.29), 192 (8.32), 105 (100.00), 77 (69.47).

Anal. Calcd. for $C_{22}H_{24}N_4O_3$ (392.45): C, 67.33; H, 6.16; N, 14.28. Found: C, 67.15; H, 6.07; N, 14.04.

Biological activity

Antileishmanial activity

Antileishmanial activity were checked for all the synthesized heterocyclic compounds and **1**–**19** were primarily screened distinctively for culture of *L. major* [28, 29]; 1 mg of every compound was dissolved using solvent DMSO (1 ml) and 1 mg of Amphotericin B was also solubilized in 1 ml of DMSO. Then, 180 µl of medium was poured in various wells of 96-well plates. Also, 20 µl of the tetrahydroquinoline derivatives solution was then added into the medium and diluted serially. Parasites at log phase for 3 min were centrifuged at 3000 rpm. Fresh culture medium was used for diluting the parasites to a final density of 2×10^6 cells/ml. In all wells, 100 µl of parasite culture was added. Negative and standard drugs were maintained having DMSO and Amphotericin B. For positive and negative controls, three rows were left empty. DMSO was diluted serially in medium in case of negative controls while in positive control there were different concentrations of standard antileishmanial compound, e.g., Amphotericin B. Microtiter plates were incubated for 72 h at 24 °C. Every assay was in duplicate. Then 15 µl of test culture was transferred after 72 h, for growth in a Neubauer counting chamber and live promastigotes were counted using a light microscope.

Cytotoxicity activity by brine-shrimp lethality assay

The brine shrimp cytotoxicity assay was used by following the procedure described [30]. By dissolving 34 g of sea salt (Aquarium System, OH, UISA) in 1000 ml of distilled water with regular stirring then artificial sea water was prepared. Forceful shaking on a magnetic stirrer was done to verify the solution in an open beaker for two hours. Then 50 mg of *Artemia salina* Leach eggs (Artemia, Inc., CA, USA) was added in a hatching chamber. Seawater was used for hatching of *Artemia salina* in a shallow quadrilateral dish (22 × 32 cm) previously filled with prepared (brine shrimp eggs) which comprised two compartments, one was large and the other was a small compartment. Both the compartments were separated by a wall consisting of several holes of 2 mm in diameter, with artificial sea water in the large compartment on which eggs were spread on the surface. The large compartment was covered with aluminum foil so that there was darkness in that compartment. The smaller compartment was lit with a lamp. After 24–26 h the hatching process started and the newly hatched nauplii (brine shrimp larvae) traveled towards the smaller compartment due to the presence of light. The nauplii were collected in a beaker with the help of a Pasteur pipette. Three concentrations of the tested samples were dissolved in methanol (10, 100 and 1000 µg/ml) and were used against brine shrimp larvae; the vials and the control containing 500 µl of solvent were allowed to evaporate to dryness in about 48 h at room temperature and then the rate of death at all concentrations was

observed. To check the number of deaths, each sample quantity taken was 0.5 ml in a 20 ml vial. Furthermore, additional 2 ml artificial sea water was added to evaporate the solvent. After this 30 shrimp were transferred to each vial with final volume adjusted to 5 ml. They were kept under florescence lighting at a temperature of 25 °C for a time period of 24 h. Three replicates were prepared for each dose level. The negative control solution was the same saline solution used to prepare the stock test sample solution. Potassium dichromate was used as standard toxicant and dissolved in artificial seawater, to obtain concentrations of 1000, 100, and 10 ppm. A Finney computer program was used to evaluate ED50 after the percentage survival was calculated.

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References

1. O.I. Abd El-Salam, D.A. Abou Ella, N.S. Ismail, M. Abdullah, Pharmazie **64**(3), 147 (2009)
2. K. Tsuji, G.W. Spears, K. Nakamura, T. Tojo, N. Seki, A. Sugiyama, M. Matsuo, Bioorg. Med. Chem. Lett. **12**(1), 85 (2002)
3. I. Tomasoli, M. Pudlo, C. de Los Rios, E. Soriano, I. Colmena, L. Gandia, L. Rivas, A. Samadi, J. Marco-Contelles, B. Refouvelet, Eur. J. Med. Chem. **46**, 1 (2011)
4. M.M. Ghorab, F.A. Ragab, M.M. Hamed, Eur. J. Med. Chem. **44**, 4211 (2009)
5. S.I. Alquasoumi, A.M. Al-Taweel, A.M. Alafeefy, M.M. Ghorab, E. Noaman, Eur. J. Med. Chem. **45**(5), 1849 (2010)
6. N. Yamada, S. Kadowaki, K. Takahashi, K. Umezu, Biochem. Pharmacol. **44**, 1211 (1992)
7. D.S. Su, J.J. Lim, E. Tinney, B.L. Wan, M.B. Young, K.D. Anderson, D. Rudd, V. Munshi, C. Bahnck, Bioorg. Med. Chem. Lett. **19**, 5119 (2009)
8. R.T. Skerlj, G.J. Bridger, A. Kaller, E.J. McEachern, J.B. Crawford, Y. Zhou, J. Med. Chem. **53**, 3376 (2010)
9. C. Ramesh, T.K. Nayak, R. Burai, M.K. Dennis, H.J. Hathaway, L.A. Sklar, E.R. Prossnitz, J.B. Arterburn, J. Med. Chem. **53**, 1004 (2010)
10. H.F. de Freitas, M.S. Castilho, Med. Chem. **8**(2), 252 (2012)
11. T.A. Rano, E. Sieber-McMaster, P.D. Pelton, M. Yang, K.T. Demarest, G.H. Kuo, Bioorg. Med. Chem. Lett. **19**, 2456 (2009)
12. S. Prafulla, P. Pratik, K. Prabhjot, AJRC **6**, 599 (2013)
13. H.S. Kim, H.J. Gim, M. Yang, J.H. Ryu, R. Jeon, Heterocycles **71**, 2131 (2007)
14. G. Dorey, B. Lockhart, P. Lestage, P. Casara, Bioorg. Med. Chem. Lett. **10**, 935 (2000)
15. D.K. Dodiya, H.K. Ram, A.R. Trivedi, V.H. Shah, J. Serb. Chem. Soc. **76**(6), 823 (2011)
16. H.M. Faidallah, A.A. Saqer, K.A. Alamry, K.A. Khan, A.M. Asiri, J. Enzyme Inhib. Med. Chem. **29**(3), 367 (2014)
17. H.M.F. Madkour, M.A.E.M. El-Hashash, M.S. Salem, A.O.A. Mahmoud, Y.M.A.S. Al-Qahraman, J. Heterocyclic Chem. (2017). https://doi.org/10.1002/jhet.3046
18. M.S. Salem, M.A.M. Ali, Biol. Pharm. Bull. **39**, 473 (2016)
19. M.S. Salem, M. Farhat, A.O. Errayes, H.M.F. Madkour, Chem. Pharm. Bull. **63**, 866 (2015)
20. M.S. Salem, A.O. Errayes, J. Chem. Res. **40**, 299 (2016)
21. M.S. Salem, S.I. Sakr, W.M. El-Senousy, H.M.F. Madkour, Arch. Pharm. Chem. Life Sci. **346**, 766 (2013)
22. I.H. Eissa, A.M. El-Naggar, M.A. El-Hashash, Bioorg. Chem. **67**, 43 (2016)
23. M. El-Kady, E.M.H. Abbas, M.S. Salem, A.F.M. Kassem, S.I. Abd, El-Moez. Res. Chem. Intermed. **42**, 3333 (2016)
24. K. Saito, S. Kambe, A. Sakurai, H. Midorikawa, Synthesis (1981). https://doi.org/10.1055/s-1981-29388

25. D.R. Anderson, N.W. Stehle, S.A. Kolodziej, E.J. Reinhard, L.F. Lee, United States Patent Application 20040142978, July 22 (2004)
26. E.J. Reinhard, S.A. Kolodziej, D.R. Anderson, N.W. Stehle, W.F. Vernier, L.F. Lee, S.G. Hegde, United States Patent Application 20040127519, July 1 (2004)
27. M.H. Abdel-Lattif, M.I. Kobeasy, ShH Abdel-Hafez, Int. J. Basic Appl. Sci. **3**(4), 433 (2014)
28. Y.M. Al-Kahraman, H.M.F. Madkour, D. Ali, M. Yasinzai, Molecules **15**, 660 (2010)
29. G.S. Singh, Y.M.S.A. Al-Kahraman, D. Mpadi, M. Yasinzai, Bioorg. Med. Chem. Lett. **22**, 5704 (2012)
30. G.S. Singh, Y.M.S.A. Al-Kahraman, D. Mpadi, M. Yasinzai, Med. Chem. **10**, 382 (2014)