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ORIGINAL PAPER

Synthesis and anti-arrhythmic activity of some piperidine-based 1,3-thiazole, 1,3,4-thiadiazole, and 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives

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Abstract The reaction of 1-[4-(piperidin-1-yl)benzylidene] thiosemicarbazide with hydrazonoyl chlorides afforded 1,3-thiazole derivatives. Cyclization of two compounds of the latter 1,3-thiazole by means of bromine in the presence of sodium acetate at room temperature gave 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives. The reaction of 2-cyano-3-(4-piperidin-1-ylphenyl)prop-2-enethioamide with hydrazonoyl chlorides under reflux in ethanol in the presence of triethylamine yielded 1,3-thiazoles. Treatment of 3-oxo-3-(piperidin-1-yl)propanenitrile with phenyl isothiocyanate in DMF, in the presence of KOH, at ambient temperature, resulted in the formation of 3-anilino-3-mercapto-2-(piperidin-1-ylcarbonyl)acrylonitrile which was reacted with hydrazonoyl chlorides to yield the corresponding 1,3,4-thiadiazole derivatives. Some of the newly synthesized compounds had significant anti-arrhythmic activity.

Keywords Heterocycles · Cyclizations · 1,3-Thiazole · 1,3,4-Thiadiazole · Anti-arrhythmic activity

Introduction

In the course of our research efforts towards the preparation of new biologically active heterocycles [1–6] specifically 1,3-thiazoles [1] and 1,3,4-thiadiazoles [2], we have reported that some of the newly synthesized heterocycles had antihypertensive [1], antibacterial [2–4], antifungal [5], and anti-arrhythmic [6] activities. On the other hand, piperidines are an important class of heterocycles found in numerous natural products and medicinal structures [7], such as raloxifene [8] and thioridazine [9]. The piperidine moiety is also part of the well known vasodilator minoxidil (Fig. 1), which is used to treat high blood pressure and androgenetic alopecia in men [10]. Furthermore, 1,3-thiazole has interesting pharmacological properties [11] and is a key structural component of several drugs. For example, clomethiazole (Fig. 1) is a potent sedative and hypnotic drug [12] containing the 1,3-thiazole moiety.

Moreover, some 1,3,4-thiadiazole derivatives are highly potent inhibitors of HIV-1 [13] and useful as anti-inflammatory agents [14]. In addition, 1,3,4-thiadiazole is a common structural feature in many biologically active molecules, for example methazolamide (Fig. 1), which is used clinically in the treatment of some forms of epilepsy [15]. In the light of previous information, we wish to report herein the utility of 4-piperidin-1-ylbenzaldehyde (**1**) and 3-oxo-3-(piperidin-1-yl)propanenitrile (**11**) in the synthesis of some piperidine-based polyfunctional 1,3-thiazole, 1,3,4-thiadiazole, and 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives to evaluate their anti-arrhythmic activity.

Results and discussion

Chemistry

4-Piperidin-1-ylbenzaldehyde (**1**) was prepared by reaction of 4-fluorobenzaldehyde and piperidine in *DMSO*, in the presence of K_2CO_3 [16]. The reaction of the latter aldehyde with thiosemicarbazide in ethanol under reflux afforded

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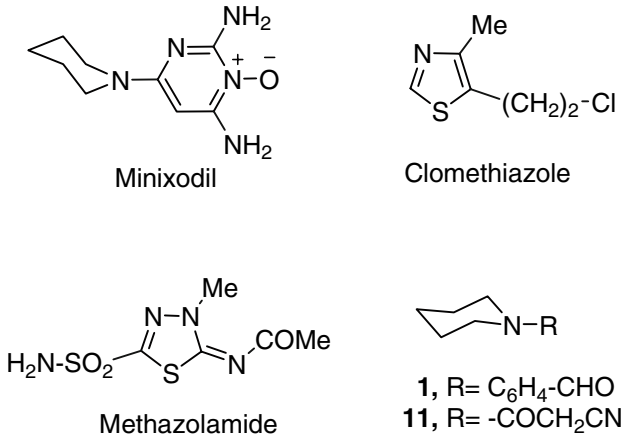
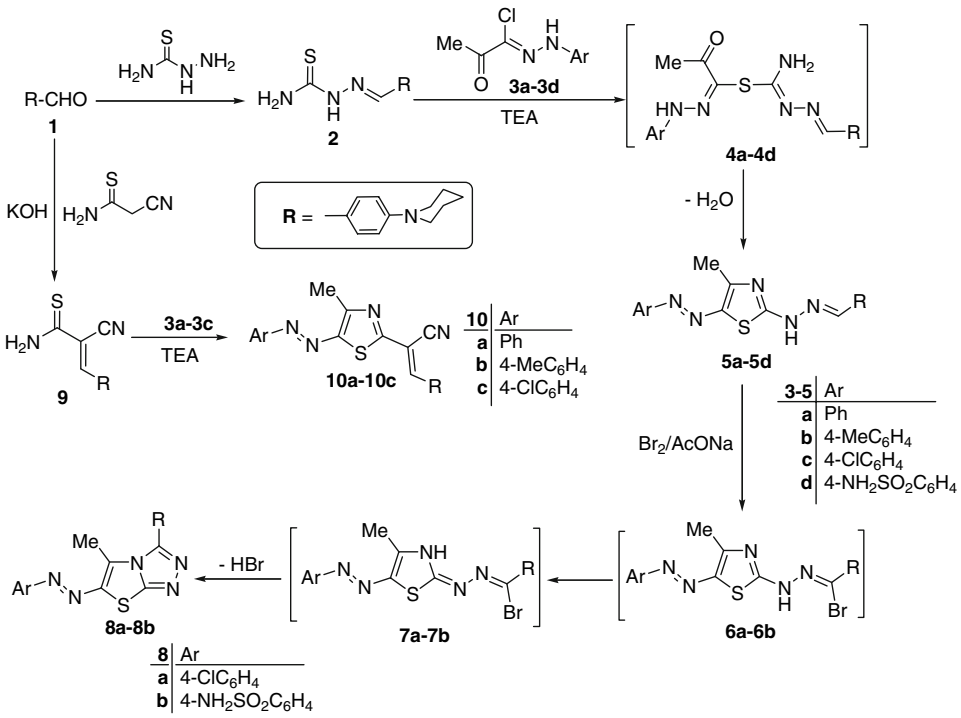


Fig. 1 Structures of some compounds mentioned in the "Introduction"

1-[4-(piperidin-1-yl)benzylidene]thiosemicarbazide (**2**) [17]. Compound **2** reacted with hydrazonoyl chloride **3a**–**3d** in ethanol under reflux, in the presence of a catalytic amount of triethylamine, to yield products formulated as **5a**–**5d** through the non-isolable intermediate **4a**–**4d** (Scheme 1). The IR spectra of the isolated compounds revealed, in each case, an absorption band of an NH function near 2,233–3,219 cm^{-1} and their ^1H NMR spectra contained, in each case, a singlet in the region δ 8.47–8.68 ppm due to the –CH=N– proton, in addition to the D_2O-exchangeable signal of NH protons in the region δ 10.32–10.64 ppm. 1,5 Electrocyclization [18, 19] of hydrazone **5c** or **5d** by treatment with bromine in acetic acid, in the presence of sodium acetate, at room temperature, formed the non-isolable intermediate hydrazonoyl bromides **6a** and **6b**, which underwent in-situ dehydrobromination under reaction conditions to give the corresponding 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives **8a** and **8b** as end products (Scheme 1).

Next, the catalytic condensation reaction of 4-piperidin-1-ylbenzaldehyde (**1**) with 2-cyanoethanethioamide afforded 2-cyano-3-(4-piperidin-1-ylphenyl)prop-2-enethioamide (**9**) in moderate yield by use of either potassium hydroxide at ambient temperature or piperidine in ethanol under reflux. The IR spectrum of compound **9** exhibited characteristic broad amino bands at 3,362 and 3,272 cm^{-1} while the sharp nitrile band was observed at 2,207 cm^{-1}. Its ^1H NMR spectrum contained a D_2O-exchangeable signal of the amino function at 9.15 ppm and the singlet signal of an olefinic proton at 8.03 ppm, in addition to the signals of piperidine protons in the regions δ 1.57–1.60 (6H) and δ 3.44–3.47 (4H) ppm. Also it showed the two doublets of the A_2B_2 system for the *p*-substituted benzene ring at 7.03 and 7.86 ppm with J = 9.0 Hz. Treatment of 2-cyano-3-(4-piperidin-1-ylphenyl)prop-2-enethioamide (**9**) with the hydrazonoyl chlorides **3a**–**3c** in ethanol under reflux, in the presence of triethylamine, afforded the corresponding 1,3-thiazole derivatives **10a**–**10c** (Scheme 1). The IR spectra of **10a**–**10c** showed, in each case, the sharp absorption band near 2,200 cm^{-1} of the nitrile function, and their mass spectra revealed, in each case, a peak corresponding to their molecular ion.

Scheme 1



The reaction of 3-oxo-3-(piperidin-1-yl)propanenitrile (**11**) [20] with phenyl isothiocyanate at ambient temperature in dimethylformamide, in the presence of potassium hydroxide, provided the non-isolable potassium salt **12**. Subsequent addition of the appropriate hydrazonoyl chloride **3a–3d** yielded the corresponding 1,3,4-thiadiazole derivatives **15a–15d** (Scheme 2). Scheme 2 depicts the possible structures proposed for the reaction products. However, elemental analysis and spectral data of the reaction products supported the 1,3,4-thiadiazole structure **15a–15d**. These results indicate that the reaction of the potassium salt **12** with hydrazonoyl chloride **3a–3d** proceeds in each case, through the non-isolable intermediate **14a–14d** which cyclized by loss of an aniline molecule to form the isolable final product 1,3,4-thiadiazole derivatives **15a–15d** [2].

On the other hand, the potassium salt **12** could be converted into 3-anilino-3-mercapto-2-(piperidin-1-ylcarbonyl) acrylonitrile (**13**) upon neutralization with dilute hydrochloric acid (Scheme 2). The reaction of compound **13** with hydrazonoyl chloride **3a–3d** in ethanol under reflux, in the presence of catalytic amount of triethylamine, resulted in the formation of the products identical in all respects with those obtained from the method described above. The IR spectra of compounds **15a–15d** showed, in each case, the appearance of two carbonyl absorption bands in the region 1,741–1,630 cm^{-1} in addition to a characteristic nitrile absorption band in the region 2,201–2,190 cm^{-1}. Their mass spectra revealed, in each case, a peak corresponding to their molecular ion.

Pharmacological screening

Procaine amide, 5 mg/kg iv, and lidocaine, 5 mg/kg iv, led to an increase in LD_{100} by 65%, which corresponds to a LD_{100} of approximately 9 μg/100 mg. Table 1 shows compounds **2**, **5a–5d**, **9**, and **10a–10c** had no

Table 1 Anti-arrhythmic activity of the synthesized compounds (5 mg/kg)

Compound	Percentage increase (LD_{100}/%)
2	No effect
5a	No effect
5b	No effect
5c	No effect
5d	No effect
8a	No effect
8b	No effect
9	No effect
10a	No effect
10b	No effect
10c	No effect
13	38 ± 0.11
15a	72 ± 0.11
15b	74 ± 0.11
15c	79 ± 0.22
15d	66 ± 0.21

All data were significantly different from the normal control value at $P \leq 0.05$

Scheme 2

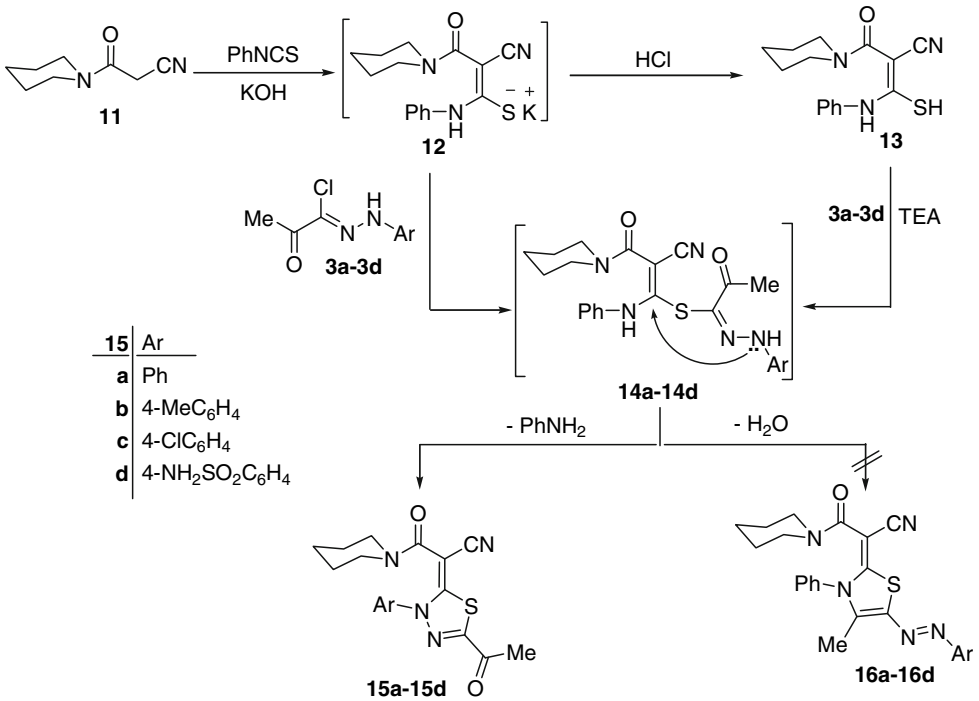


Table 2 Acute toxicity (LD_{50}) of compounds **13** and **15a–15d**

Compound	LD_{50}/mg kg^{-1}
13	898.56 ± 3.67
15a	578.33 ± 2.29
15b	897.89 ± 3.35
15c	654.11 ± 1.18
15d	675.56 ± 2.44

All data were significantly different from the normal control value at $P \leq 0.05$

anti-arrhythmic activity, whereas compound **13** had anti-arrhythmic activity less than that of procaine amide or lidocaine. Compounds **15a–15d** were more active than procaine amide or lidocaine.

Structure–activity relationship

1,3,4-Thiadiazole and piperidine moieties are essential for anti-arrhythmic activity in **15a–15d**. The chlorinated 1,3,4-thiadiazole derivative **15c** had a higher anti-arrhythmic effect than the other derivatives.

Determination of acute toxicity (LD_{50})

The LD_{50} was determined by using rats. They were injected with different, increasing doses of the synthesized compounds. The dose that killed 50% of the animals was calculated according to *Austen* and *Brocklehurst* [21] (Table 2).

Experimental

Chemistry

Melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were obtained from the microanalytical unit, Cairo University, Cairo, Egypt, their results were found to be in good agreement with the calculated values. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in deuterated dimethylsulfoxide (DMSO-d_6). Mass spectra were measured on a Varian MAT CH-5 spectrometer (70 eV). Hydrazonoyl chlorides **3a–3c** [22] and **3d** [23] were prepared according to reported methods.

*4-Piperidin-1-ylbenzaldehyde (**1**)*
mp = 65–66 °C [Lit. mp = 62–64 °C] [16]; the IR, mass, and ^{1}H NMR spectra of compound **1** were found to be identical with those described in Ref. [16].

*1-[4-(Piperidin-1-yl)benzylidene]thiosemicarbazide (**2**)*
mp = 105–106 °C [Lit. mp = 105–106 °C] [17]; the IR, mass, and ^{1}H NMR spectra of compound **2** were found to be identical with those described in Ref. [17].

*General procedure for reaction of thiosemicarbazone **2** with hydrazonoyl chlorides **3a–3d***

To 2.7 g compound **2** (10 mmol) dissolved in 50 cm^3 absolute ethanol, the appropriate hydrazonoyl chloride **3a–3d** (10 mmol) and 0.5 cm^3 triethylamine were added. The reaction mixture was heated under reflux for 2 h. The solid formed was isolated by filtration, washed with ethanol, and recrystallized from EtOH–DMF to afford the corresponding 1,3-thiazole derivatives **5a–5d**.

4-Methyl-2-{[2-(4-(piperidin-1-yl)benzylidene) hydrazino]}-5-Phenylazo-1,3-thiazole (**5a**, $C_{22}H_{24}N_6S$)
mp 215–217 °C; yield: 2.83 g (70%) starting from 1.97 g (10 mmol) **3a**; IR (KBr): $\bar{\nu}$ = 3,219 (NH), 1,604 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.57–1.60 (m, 6H, piperidine), 2.57 (s, 3H, CH_3), 3.32–3.35 (m, 4H, piperidine), 7.1–7.73 (m, 9H, *Ar*-H), 8.52 (s, 1H, –CH=N–), 10.61 (s, D_2O-exchangeable, 1H, NH) ppm; MS (70 eV): *m*/*z* = 405 (M^++1, 14.6), 404 (M^+, 100), 281 (24.7), 125 (47.2).

4-Methyl-2-{[2-(4-(piperidin-1-yl)benzylidene) hydrazino]}-5-(4-tolylazo)-1,3-thiazole (**5b**, $C_{23}H_{26}N_6S$)
mp 211–213 °C; yield: 3.10 g (74%) starting from 2.11 g (10 mmol) **3b**; IR (KBr): $\bar{\nu}$ = 3,233 (NH), 1,601 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.52–1.60 (m, 6H, piperidine), 2.22 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.31–3.35 (m, 4H, piperidine), 7.00–7.68 (m, 8H, *Ar*-H), 8.68 (s, 1H, –CH=N–), 10.64 (s, D_2O-exchangeable, 1H, NH) ppm; MS (70 eV): *m*/*z* = 419 (M^++1, 35.2), 418 (M^+, 100), 221 (31.5).

4-Methyl-2-{[2-(4-(piperidin-1-yl)benzylidene) hydrazino]}-5-[(4-chlorophenyl)azo]-1,3-thiazole
(**5c**, $C_{22}H_{23}ClN_6S$)
mp 233–235 °C; yield: 3.16 g (72%) starting from 2.13 g (10 mmol) **3c**; IR (KBr): $\bar{\nu}$ = 3,215 (NH), 1,600 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.58–1.60 (m, 6H, piperidine), 2.57 (s, 3H, CH_3), 3.33–3.35 (m, 4H, piperidine), 7.0–7.70 (m, 8H, *Ar*-H), 8.50 (s, 1H, –CH=N–), 10.53 (s, D_2O-exchangeable, 1H, NH) ppm; MS (70 eV): *m*/*z* = 440 (M^++2, 3.53), 439 (M^++1, 16.85), 438 (M^+, 35.73), 281 (100), 125 (30.58).

4-Methyl-2-{[2-(4-(piperidin-1-yl)benzylidene) hydrazino]}-5-[(4-aminosulfonylphenyl)azo]-1,3-thiazole
(**5d,** $C_{22}H_{25}N_7O_2S_2$)
mp 290–292 °C; yield: 3.77 g (78%) starting from 2.76 g (10 mmol) **3d**; IR (KBr): $\bar{\nu}$ = 3,307, 3,265, 3,183 (NH,

NH_2), 1,596 (C=N), 1,332, 1,151 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.58–1.61$ (m, 6H, piperidine), 2.58 (s, 3H, CH_3), 3.31–3.34 (m, 4H, piperidine), 7.25 (d, 2H, $J = 7.6$ Hz, *Ar*-H), 7. 44 (d, 2H, $J = 7.6$ Hz, Ar-H), 7.58 (d, 2H, $J = 8.7$ Hz, *Ar*-H), 7.82 (d, 2H, $J = 8.7$ Hz, *Ar*-H), 7.26 (s, D_2O-exchangeable, 2H, NH_2), 8.47 (s, 1H, –CH=N–), 10.32 (s, D_2O-exchangeable, 1H, NH) ppm; MS (70 eV): $m/z = 484$ (M^++1, 26.3), 483 (M^+, 100).

*General procedure for synthesis of [1,3]thiazolo[2,3-c][1,2,4]triazole derivatives **8a** and **8b***

Bromine (0.44 g, 5.5 mmol) in 5 cm^3 acetic acid was added drop-wise to a stirred mixture of the appropriate hydrazone **5c** or **5d** (5 mmol) and 1.2 g sodium acetate (15 mmol) in 30 cm^3 acetic acid. The reaction mixture was stirred for 12 h at room temperature. The mixture was then poured on to 250 cm^3 ice-cold water. The solid that precipitated was isolated by filtration, washed with 50 cm^3 5% sodium bicarbonate solution and then with water, dried, and crystallized from EtOH–DMF to give the 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives **8a** and **8b**.

6-[(4-Chlorophenyl)azo]-5-methyl-3-[4-(piperidin-1-yl)phenyl][1,3]thiazolo[2,3-c][1,2,4]triazole (**8a**, $C_{22}H_{21}ClN_6S$)
mp 209–211 °C; yield: 1.3 g (60%) starting from 2.2 g (5 mmol) **5c**; IR (KBr): $\bar{\nu} = 1{,}609$ (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.57–1.60$ (m, 6H, piperidine), 2.58 (s, 3H, CH_3), 3.31–3.36 (m, 4H, piperidine), 7.1–7.68 (m, 8H, *Ar*-H), ppm; MS (70 eV): $m/z = 338$ (M^++2, 7.37), 437 (M^++1, 14.22), 436 (M^+, 100).

6-[(4-Aminosulfonylphenyl)azo]-5-methyl-3-[4-(piperidin-1-yl)phenyl][1,3]thiazolo[2,3-c][1,2,4]triazole (**8b**, $C_{22}H_{23}N_7O_2S_2$)
mp 215–217 °C; yield: 1.54 g (64%) starting from 2.4 g (5 mmol) **5d**; IR (KBr): $\bar{\nu} = 3{,}414$, 3,205 (NH_2), 1,616 (C=N), 1,314, 1,160 (SO_2) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.58–1.61$ (m, 6H, piperidine), 2.58 (s, 3H, CH_3), 3.31–3.34 (m, 4H, piperidine), 7.27 (d, 2H, $J = 7.0$ Hz, *Ar*-H), 7. 40 (d, 2H, $J = 7.3$ Hz, *Ar*-H), 7.58 (d, 2H, $J = 8.7$ Hz, *Ar*-H), 7.81 (d, 2H, $J = 9.0$ Hz, *Ar*-H), 7.26 (s, D_2O-exchangeable, 2H, NH_2) ppm; MS (70 eV): $m/z = 482$ (M^++1, 8.6), 481 (M^+, 100).

2-Cyano-3-(4-piperidin-1-ylphenyl)prop-2-enethioamide (**9**, $C_{15}H_{17}N_3S$)
Method A: 4-Piperidin-1-ylbenzaldehyde (**1**) (1.89 g, 10 mmol) and 1.0 g 2-cyanoethanethioamide (10 mmol) were dissolved in 30 cm^3 ethanol. After the addition of 0.5 cm^3 10% KOH solution, the mixture was set aside for 2 h. The orange crystals were isolated by filtration and recrystallized from ethanol to give compound **9** in 75% yield.

Method B: To 1.89 g 4-piperidin-1-ylbenzaldehyde (**1**) (10 mmol) and 1.0 g 2-cyanoethanethioamide (10 mmol) in 30 cm^3 absolute ethanol, 0.5 cm^3 piperidine was added and the reaction mixture was gently heated under reflux for 1 h, then left to cool. The solid formed was isolated by filtration and crystallization from ethanol afforded a product identical in all respects with that obtained from method A, above, in 68% yield, mp 220–222 °C; IR (KBr): $\bar{\nu} = 3{,}362$, 3,272 (NH_2), 2,207 (C≡N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.57–1.60$ (m, 6H, piperidine), 3.44–3.47 (m, 4H, piperidine), 7.03 (d, 2H, $J = 9.0$ Hz, *Ar*-H), 7.86 (d, 2H, $J = 9.0$ Hz, *Ar*-H), 8.03 (s, 1H, –CH=N–), 9.15 (s, D_2O-exchangeable, 2H, NH_2) ppm; MS (70 eV): $m/z = 272$ (M^++1, 23.7), 271 (M^+, 100), 270 (80.3), 236 (41.9), 187 (14.6).

*Reaction of thioamide **9** with hydrazonoyl chlorides **10a–10c***

This reaction was carried out by the same procedure described for the synthesis of compounds **5a–5d** using thioamide **9** instead of thiosemicarbazone **2** and using hydrazonoyl chlorides **3a–3c**. After heating under reflux for 5 h, the solid product was isolated by filtration and recrystallized from aqueous DMF to afford the corresponding 1,3-thiazole derivatives **10a–10c**.

2-[4-Methyl-5-(phenylazo)-1,3-thiazol-2-yl]-3-[4-(piperidin-1-yl)phenyl]acrylonitrile (**10a**, $C_{24}H_{23}N_5S$)
mp 202–204 °C; yield: 2.61 g (63%) starting from 1.97 g (10 mmol) **3a**; IR (KBr): $\bar{\nu} = 2{,}202$ (C≡N), 1,598 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.56–1.60$ (m, 6H, piperidine), 2.55 (s, 3H, CH_3), 3.43–3.45 (m, 4H, piperidine), 6.98–7.88 (m, 9H, *Ar*-H), 8.10 (s, 1H, –CH=N–) ppm; MS (70 eV): $m/z = 414$ (M^++1, 16.4), 413 (M^+, 100), 235 (28.6), 187 (27.1).

2-[4-Methyl-5-(4-tolylazo)-1,3-thiazol-2-yl]-3-[4-(piperidin-1-yl)phenyl]acrylonitrile (**10b**, $C_{25}H_{25}N_5S$)
mp 210–212 °C; yield: 1.17 g (64%) starting from 2.11 g (10 mmol) **3b**; IR (KBr): $\bar{\nu} = 2{,}199$ (C≡N), 1,600 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.55–1.60$ (m, 6H, piperidine), 2.51 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.42–3.45 (m, 4H, piperidine), 7.01–7.83 (m, 8H, *Ar*-H), 8.10 (s, 1H, –CH=N–) ppm; MS (70 eV): $m/z = 428$ (M^++1, 21.1), 427 (M^+, 58.5), 226 (100), 196 (11.5).

2-{4-Methyl-5-[4-chlorophenyl)azo]-1,3-thiazol-2-yl}-3-[4-(piperidin-1-yl)phenyl]acrylonitrile (**10c**, $C_{24}H_{22}ClN_5S$)
mp 238–240 °C; yield: 1.17 g (60%) starting from 2.31 g (10 mmol) **3c**; IR (KBr): $\bar{\nu} = 2{,}202$ (C≡N), 1,603 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.54–1.60$

(m, 6H, piperidine), 2.54 (s, 3H, CH_3), 3.42–3.45 (m, 4H, piperidine), 7.00–7.83 (m, 8H, *Ar*-H), 8.10 (s, 1H, –CH=N–) ppm; MS (70 eV): $m/z = 448$ (M^++2, 10.4), 447 (M^++1, 13.5), 409 (M^+, 100), 236 (54.8).

*3-Oxo-3-(piperidin-1-yl)propanenitrile (**11**)*
mp = 88 °C [Lit. mp = 87 °C] [20]; the IR, mass, and ^{1}H NMR spectra of compound **11** were found to be identical with those described in Ref. [20].

3-Anilino-3-mercapto-2-(piperidin-1-ylcarbonyl) acrylonitrile (**13**, $C_{15}H_{17}N_3OS$)
To a stirred solution of 0.56 g potassium hydroxide (10 mmol) in 20 cm^3 dimethylformamide, 1.52 g 3-oxo-3-(piperidin-1-yl)propanenitrile (**11**) (10 mmol) was added. After stirring for 30 min, 1.35 g phenyl isothiocyanate (10 mmol) was added to the resulting mixture and stirring was continued for 3 h. The mixture was then poured on to crushed ice and neutralized with hydrochloric acid. The solid product that formed was isolated by filtration, washed with water, dried, and finally crystallized from ethanol to afford compound **13** as greenish yellow crystals in 78% yield, mp 160–162 °C; IR (KBr): $\bar{\nu} = 3{,}238$ (NH), 2195 (C≡N), 1634 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.47$–1.67 (m, 6H, piperidine), 4.12–4.36 (m, 4H, piperidine), 6.50–7.78 (m, 5H, *Ar*-H), 11.95 (s, D_2O-exchangeable, 1H, NH), 12.71 (s, D_2O-exchangeable, 1H, SH) ppm; MS (70 eV): $m/z = 288$ (M^++1, 20.7), 287 (M^+, 27.8), 254 (32.3), 152 (100), 111 (18.2).

*Synthesis of 2-(5-acetyl-3-aryl-1,3,4-thiadiazol-2(3H)-ylidene)-3-oxo-3-piperidin-1-ylpropanenitrile **15a–15d***

Method A: To a stirred solution of 0.06 g potassium hydroxide (1 mmol) in 20 cm^3 dimethylformamide, 1.52 g 3-oxo-3-(piperidin-1-yl)propanenitrile (**11**) (10 mmol) was added. After stirring for 30 min, 0.14 g phenyl isothiocyanate (1 mmol) was added to the resulting mixture. Stirring was continued for 3 h then the appropriate hydrazonoyl chloride **3a–3d** (1 mmol) was added portion-wise over a period of 30 min. When addition was complete, the reaction mixture was stirred for 12 h while the hydrazonoyl chloride dissolved and a yellowish colored product precipitated. The solid product was isolated by filtration, washed with ethanol, and finally recrystallized from EtOH–DMF to afford the corresponding 1,3,4-thiadiazole derivative **15a–15d**.

Method B: To 0.29 g compound **13** (1 mmol) in 30 cm^3 ethanol the appropriate hydrazonoyl chloride **3a–3d** (1 mmol) and 0.5 cm^3 triethylamine were added. The mixture was heated under reflux for 2 h, and the solid formed was isolated by filtration, washed with water, and dried. Crystallization from EtOH–DMF afforded compounds **15a–15d**.

2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-oxo-3-piperidin-1-ylpropanenitrile (**15a**, $C_{18}H_{18}N_4O_2S$)
mp 198–200 °C; yield: 2.41 g (68%) starting from 1.97 g (10 mmol) **3a**; IR (KBr): $\bar{\nu} = 2{,}198$ (C≡N), 1,675, 1,628 (2C=O), 1,596 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.35$ (s, 3H, CH_3), 1.47–1.49 (m, 6H, piperidine), 4.16–4.35 (m, 4H, piperidine), 6.50–7.72 (m, 5H, *Ar*-H) ppm; MS (70 eV): $m/z = 355$ (M^++1, 22.5), 354 (M^+, 100).

2-[5-Acetyl-3-(4-tolyl)-1,3,4-thiadiazol-2(3H)-ylidene]-3-oxo-3-piperidin-1-ylpropanenitrile (**15b**, $C_{19}H_{20}N_4O_2S$)
mp 216–218 °C; yield: 2.7 g (73%) starting from 2.11 g (10 mmol) **3b**; IR (KBr): $\bar{\nu} = 2{,}190$ (C≡N), 1,666, 1,630 (2C=O), 1,596 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.49$–1.67 (m, 6H, piperidine), 2.47 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.11–4.36 (m, 4H, piperidine), 7.22 (d, 2H, $J = 8.7$ Hz, *Ar*-H), 7.94 (d, 2H, $J = 9.0$ Hz, *Ar*-H) ppm; MS (70 eV): $m/z = 368$ (M^+, 2.2), 261 (100), 208 (21.3), 132 (20.6), 106 (44.9).

2-[5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene]-3-oxo-3-piperidin-1-ylpropanenitrile
(**15c**, $C_{18}H_{17}ClN_4O_2S$)
mp 250–252 °C; yield: 2.72 g (70%) starting from 2.31 g (10 mmol) **3c**; IR (KBr): $\bar{\nu} = 2{,}192$ (C≡N), 1,679, 1,634 (2C=O), 1,601 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.51$ (m, 6H, piperidine), 1.64 (m, 4H, piperidine), 2.37 (s, 3H, CH_3), 7.10 (d, 2H, $J = 9.0$ Hz, *Ar*-H), 7.73 (d, 2H, $J = 9.0$ Hz, *Ar*-H) ppm; MS (70 eV): $m/z = 389$ (M^++1, 41.5), 388 (M^+, 100), 311 (12.8), 249 (24.1).

2-[5-Acetyl-3-(4-aminosulfonylphenyl)-1,3,4-thiadiazol-2(3H)-ylidene]-3-oxo-3-piperidin-1-ylpropanenitrile
(**15d**, $C_{18}H_{19}N_5O_4S_2$)
mp 220–222 °C; yield: 2.95 g (68%) starting from 2.78 g (10 mmol) **3c**; IR (KBr): $\bar{\nu} = 3{,}421$, 3,210 (NH_2), 2,192 (C≡N), 1,741, 1,680 (2C=O), 1,597 (C=N), 1,420, 1,276 (SO_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.47$–1.56 (m, 6H, piperidine), 2.29 (s, 3H, CH_3), 3.92–3.93 (m, 4H, piperidine), 7.63 (s, D_2O-exchangeable, 2H, NH_2), 7.66 (d, 2H, $J = 8.7$ Hz, *Ar*-H), 7.70 (d, 2H, $J = 8.7$ Hz, Ar-H), ppm; MS (70 eV): $m/z = 434$ (M^++1, 13.6), 433 (M^+, 45.5), 339 (100), 285 (64.6).

Anti-arrhythmic activity [24–29]

The plant alkaloid aconitine persistently activates sodium channels. Infusion of aconitine into anesthetized rats causes ventricular arrhythmias. Drugs considered to have anti-arrhythmic properties can be tested in aconitine-intoxicated rats.

Procedure

Male Ivanovas rats weighing 300–350 g were used. The animals were anesthetized by intraperitoneal injection of 1.25 g/kg urethane, 5 mg/kg aconitine dissolved in 0.1 N HNO_3 was administered by continuous infusion into the saphenous vein at 0.1 cm^3/min, and the ECG in lead II was recorded every 30 s. The test compound was injected iv at a screening dose of 3 mg/kg 5 min before the start of aconitine infusion. Twenty-four animals were used per compound.

Evaluation

The anti-arrhythmic effect of a test compound was measured by the amount of aconitine/100 g animal (duration of infusion) which induces:

- ventricular extra systoles,
- ventricular tachycardia,
- ventricular fibrillation.

Higher doses of aconitine in the treated group compared with an untreated control group are an indication of anti-arrhythmic activity. The statistical significance of differences between the groups was assessed by use of Student's *t* test.

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