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Design, synthesis, characterization, antibacterial and antifungal activities of a novel class of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles

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Abstract
Compound **26** is more potent against *Escherichia coli.* and **24** is more active against *Staphylococcus aureus, β-Heamolytic streptococcus, Vibreo cholerae, Salmonella typhii,* and *Shigella flexneri* than the standard drug ciprofloxacin. Moreover, of all the compounds tested, **26** is more effective against *Aspergillus flavus and Mucor*, than the standard drug fluconazole.

Keywords: *3,3-dimethyl-2,6-diarylpiperidin-4-one, 1,2,3-selenadiazoles, selenium dioxide, antibacterial activity, antifungal activity*

Introduction

Heterocyclic compounds are synthetically challenging ones as models for a number of physiologically active natural products. It is well known that a number of heterocyclic compounds containing nitrogen, sulfur and selenium possess different pharmacophoric properties [1–3]. However, reports about selenium-containing heterocycles are scanty, [4,5] although some of them are used as chemotherapeutic agents [1,6].

Heterocyclic ring systems having a piperidin-4-one nucleus have aroused great interest in the past and recent years due to their wide variety of biological properties such as antiviral, antitumour [7,8], central nervous system [9], local anesthetic [10], anticancer [11], and antimicrobial activity [12] and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists [13], analgesic and anti-hypertensive agents [14].

In continuation of our earlier work on 3-alkyl-2,6-diarylpiperidin-4-ones derivatives [15,16], we wish to report the development of selenadiazoles on 3,3-dimethyl-2,6-diarylpiperidin-4-ones which possess α-keto methylene group thus paving the way for a novel class of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles.

Experimental

Microbiology

Materials. All the bacterial strains namely *Staphylococcus aureus*, *β-Heamolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhii*, *Shigella flexneri*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas* and fungal strains namely *Aspergillus flavus*, *Mucor*, *Rhizopus* and *Microsporum gypsuem* were obtained from Faculty of Medicine, Annamalai University, Annamalainagar-608 002, Tamil Nadu, India.

In vitro antibacterial and antifungal activity. The *in vitro* activities of the compounds were tested in Sabourauds dextrose broth (SDB) (Hi-media, Mumbai) for fungi and nutrient broth (NB) (Hi-media, Mumbai) for bacteria by the Disc Diffusion method following the reported method. [17] The respective hydrochlorides of the test compounds **23–27** were dissolved in water

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to obtain 1 mg mL^{-1} stock solution and the different concentrations (100, 200, 500 ppm) were prepared from the stock solution. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, Mumbai) at 37 ± 1°C while fungal spores from 1 to 7 days old Sabourauds agar (Hi-media, Mumbai) slant cultures were suspended in SDB. Sterile paper disc of 5 mm diameter was saturated with the three different concentrations and such discs were placed in each seeded agar plates. The petri plates were incubated in BOD incubator at 37°C for bacteria and at 28°C for fungi. The zone of inhibition was recorded by visual observations after 24 h of inhibition for bacteria and after 72–96 h of inhibition for fungi. Moreover, the zone of inhibition was measured by excluding the diameter of the paper disc. Ciprofloxacin was used as standard for bacteria and fluconazole as standard for fungi under analogous conditions.

Chemistry

TLC was performed to assess the reactions and the purity of the products. All the reported melting points were taken in open capillaries and were uncorrected. IR spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar–360 FT-IR spectrophotometer and noteworthy absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using $CDCl_3$ as solvent. The ESI + ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on a Carlo Erba 1106 CHN analyzer.

By adopting the literature procedure, [18] 3,3-dimethyl-2,6-diarylpiperidin-4-ones **13–17** were prepared.

*General method of preparation of 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones **18–22***. A mixture of 3,3-dimethyl-2,6-diarylpiperidin-4-one (0.01 mol), semicarbazide hydrochloride (0.01 mol) and sodium acetate (0.02 mol) in ethanol (40 mL) was refluxed on a steam bath for 30 min and was concentrated to one-third of its original volume. After cooling, the mixture was poured over crushed ice. The solid product thus obtained was filtered off and recrystallized twice from ethanol to give 3,3-dimethyl-2,6-diarylpiperidin-4-one semicarbazones as crystalline solid.

*Typical procedure for the synthesis of 5,7-diphenyl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazole **23***. A solution of 3,3-dimethyl-2,6-diphenylpiperidin-4-one semicarbazone **18** (0.005 mol) in acetic acid (45 mL) was treated with selenium dioxide (0.01 mol) and stirred for 1 h at 60°C. The reaction mixture was cooled, filtered and then poured over crushed ice. The product was purified by column chromatography using ethyl acetate: petroleum ether (40:60) in the ratio 2:8 as eluent. IR (KBr) (cm^{-1}): 3306, 3065, 3033, 2969, 2927, 2880, 2798, 1585, 682, 765, 700; ^1H NMR (δ ppm): 1.25 (s, 3H, CH_3 at C-4), 1.70 (s, 3H, CH_3 at C-4), 1.94 (s, 1H, H_6); 4.80 (s, 1H, H_5), 5.39 (s, 1H, H_7), 7.22–7.60 (m, 10H, H_{arom}); ^{13}C NMR (δ ppm): 26.5 CH_3 at C-4, 28.1 CH_3 at C-4, 37.5 C-4, 69.5 C-5, 73.9 C-7, 140.4, 142.8 *ipso*-C, 159.1 C-8, 170.5 C-9, 126.9–128.8 $-C_{arom}$.

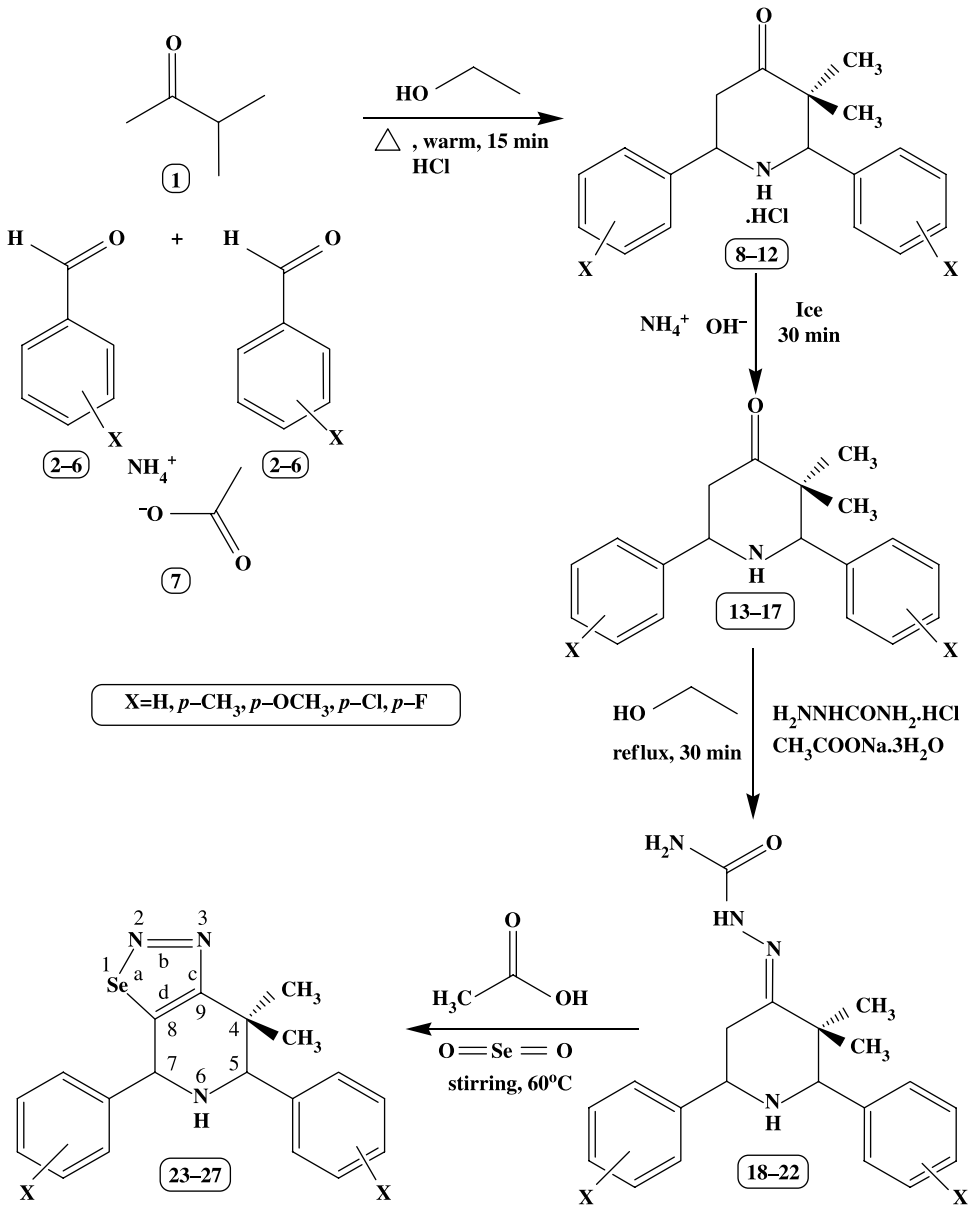
Compounds **24–27** were synthesized likewise.

*5,7-Bis(p-methylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazole **24***. IR (KBr) (cm^{-1}): 3300, 3022, 2965, 2923, 2854, 1580, 818,670; ^1H NMR (δ ppm): 1.20 (s, 3H, CH_3 at C-4), 1.71 (s, 3H, CH_3 at C-4), 2.27 (s, 1H, H_6); 2.35 (s, 6H, CH_3 at Arom. ring), 4.83 (s, 1H, H_5), 5.41 (s, 1H, H_7), 7.14–7.28 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 21.1 CH_3 at Arom. ring, 26.8 CH_3 at C-4, 28.1 CH_3 at C-4, 37.5 C-4, 68.2 C-5, 73.5 C-7, 134.9, 137.2, 141.5, 142.6 *ipso*-C, 158.9 C-8, 170.5 C-9, 127.0–129.4 $-C_{arom}$.

*5,7-Bis(p-methoxylphenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazole **25***. IR (KBr) (cm^{-1}):3315, 2959, 2925, 2923, 1578, 831, 668; ^1H NMR (δ ppm): 1.38 (s, 3H, CH_3 at C-4), 1.54 (s, 3H, CH_3 at C-4), 2.35 (s, 1H, H_6); 3.81 (s, 6H, OCH_3 at Arom. ring), 4.79 (s, 1H, H_5), 5.34 (s, 1H, H_7), 7.22–7.44 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 24.5 CH_3 at C-4, 25.6 CH_3 at C-4, 37.7 C-4, 55.2, 55.5 -OCH_3 at Arom. ring, 68.0 C-5, 73.2 C-7, 130.2, 131.9, 159.1, 159.7 *ipso*-C, 158.5 C-8, 170.5 C-9, 113.8–129.7 $-C_{arom}$.

*5,7-Bis(p-chlorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazole **26***. IR (KBr) (cm^{-1}): 3322, 3297, 2929, 2863, 1588, 834, 676; ^1H NMR (δ ppm): 1.20 (s, 3H, CH_3 at C-4), 1.72 (s, 3H, CH_3 at C-4), 2.16 (s, 1H, H_6), 4.49 (s, 1H, H_5), 5.06 (s, 1H, H_7), 7.22-7.48 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.1 CH_3 at C-4, 28.2 CH_3 at C-4, 37.5 C-4, 68.8 C-5, 73.2 C-7, 133.4, 136.6, 137.2, 138.5 *ipso*-C, 158.5 C-8, 170.8 C-9, 128.1-130.7 $-C_{arom}$.

*5,7-Bis(p-fluorophenyl)-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazole **27***. IR (KBr) (cm^{-1}): 3320, 3293, 2924, 2859, 1579, 1201, 823, 671; ^1H NMR (δ ppm): 1.23 (s, 3H, CH_3 at C-4), 1.77 (s, 3H, CH_3 at C-4), 2.19 (s, 1H, H_6), 4.51 (s, 1H, H_5), 5.09 (s, 1H, H_7), 7.28–7.51 (m, 8H, H_{arom}); ^{13}C NMR (δ ppm): 26.7 CH_3 at C-4, 28.4 CH_3 at C-4, 37.9 C-4, 69.1 C-5, 73.5 C-7, 134.4, 137.1, 138.7, 139.5 *ipso*-C, 159.3 C-8, 171.3 C-9, 129.5–131.6 $-C_{arom}$.



Scheme 1. Reaction pathway for the synthesis of novel bioactive 5,7-Diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles.

Table I. Analytical data for compounds 23–27.

Compound	Yield (%)	m.p° C	Elemental analysis (%) C Found (calculated)	H Found (calculated)	N Found (calculated)	m/z ($M^{+\cdot}$) Molecular formula
23	60	97–98	61.91 (61.96)	5.17 (5.20)	11.44 (11.41)	(369) $C_{19}H_{19}N_3Se$
24	56	100–101	63.60 (63.63)	5.81 (5.85)	10.58 (10.60)	(397) $C_{21}H_{23}N_3Se$
25	58	106–108	58.85 (58.88)	5.37 (5.41)	9.79 (9.81)	(429) $C_{21}H_{23}N_3O_2Se$
26	60	110–112	52.13 (52.19)	3.90 (3.92)	9.57 (9.61)	(438) $C_{19}H_{17}Cl_2N_3Se$
27	64	119–121	56.41 (56.44)	4.21 (4.24)	10.35 (10.39)	(405)$C_{19}H_{17}F_2N_3Se$

Results and discussion

Chemistry

The only available method for the synthesis of the target molecule is the conversion of semicarbazones of the respective 3,3-dimethyl-2,6-diarylpiperidin-4-one by selenium dioxide in acetic acid medium. The schematic representation and analytical data for the synthesized compounds **23–27** are given in Scheme–1 and Table–I respectively. A four-step synthetic strategy yielded the novel class of compounds **23–27**. A mixture of 3-methyl-butan-2-one **1**, appropriate benzaldehyde **2–6** and ammonium acetate **7** in the ratio of 1:2:1, was warmed for 15 min. and hydrochloric acid was added to afford 3,3,-dimethyl-2,6-diaryl-piperidin-4-ones hydrochloride **8–12**, which upon neutralization with aqueous ammonia at 0°C gave the respective 3,3,-dimethyl-2,6-diaryl-piperidin-4-ones **13–17**. Piperidones were converted into their semicarbazones **18–22** and were eventually cyclized into 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **23–27** using selenium dioxide in acetic acid medium. The structures of the compounds was elucidated by elemental analysis, MS, FT-IR, NMR (^{1}H & ^{13}C) spectroscopic data. The mechanistic pathway for the conversion of semicarbazones into 1,2,3-selenadiazoles is consistent with a one already reported for similar cyclisations [19].

Antibacterial activity

All the newly synthesized novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **23–27** were tested for their antibacterial activity *in vitro* (Table–II) against *S. aureus, β-H. streptococcus, V. cholerae, S. typhii, S. flexneri, E. coli, K. pneumonia* and *Pseudomonas*. Ciprofloxacin was used as standard drug; whose zone of inhibition (mm) values for *S. aureus, β-H. streptococcus, V. cholerae, S. typhii, S. flexneri, E. coli, K. pneumonia* and *Pseudomonas was 25, 28, 23, 22, 23, 24, 26 and 23 mm, respectively.* In general all the synthesized novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **23–27** exerted a wide range of modest antibacterial activity *in vitro* against the tested organisms. All the compounds **23–27** were active against all the tested bacterial strains. Compound **26** was more potent against *E. coli.* Compound **24** was more active against *S. aureus, β-H. streptococcus, V. cholerae, S. typhii,* and *S. flexneri* than the standard drug ciprofloxacin. Minimum inhibitory concentration (MIC) value in μg/mL for **26** was 6.25 for *E. coli.* MIC values for **24**, were 12.50, 6.25, 12.50, 12.50 and 6.25 for *S. aureus, β-H. streptococcus, V. cholerae, S. typhii,* and *S. flexneri,* respectively.

Table II. *In vitro* profile of compounds 23–27 against test bacteria and fungi.

	Compound 23			**Compound 24**			**Compound 25**			**Compound 26**			**Compound 27**		
Micro organisms	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm	100 ppm	200 ppm	500 ppm
S. aureus	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+
B-H.streptococcus	–	+	+	–	+	+	–	+	+	–	+	+	–	+	+
V. cholerae	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
S. typhii	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
S. flexneri	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
E. coli	–	+	+	–	+	+	–	+	+	–	+	+	–	+	+
K. pneumonia	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Pseudomonas	+	+	+	–	+	+	–	+	+	–	+	+	–	+	+
A. flavus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucor	–	+	+	–	+	+	+	+	+	–	+	+	–	+	+
Rhizopus	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+
M. gypsuem	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+

(–) = inactive, (+) = weakly active (12–16 mm), (+)(+) = moderately active (17–21 mm), (+)(+)(+) = strongly active (22–29), (+)(+)(+)(+) = highly active (30–33).

Antifungal activity

The *in vitro* antifungal activity (Table–II) of the synthesized novel heterocyclic compounds, **23–27** was studied against the fungal strains viz., *A. flavus, Mucor, Rhizopus* and *M. gypsuem.* Fluconazole was used as a standard drug whose zone of inhibition (mm) values for *A. flavus, Mucor, Rhizopus* and *M. gypsuem* was 20 ± 0.5 (mm) against all the tested fungi. In general, all the synthesized compounds exerted a wide range of modest *in vitro* antifungal activity against all the tested organisms. Moreover, of all the compounds tested, compound **26** was more effective against *A. flavus and Mucor*, than the standard drug fluconazole. MIC values in μg/mL for compound **26** were 25.0 and 12.5 for *A. flavus and Mucor* respectively.

Conclusion

A close examination of the *in vitro* antibacterial and antifungal activity profile of the differently substituted novel 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles **23–27** against the tested bacterial the fungal strains provides a structure-activity relationship which may be summarized as follows:

Results of this study show that the nature of substituent on the phenyl ring viz., chloro-as well as methoxy-functions at the *para* positions of the aryl moieties are determinant for the nature and extent of the activity of the synthesized compounds. The method of action of these compounds is unknown. These observations may promote a further development of this group of 5,7-diaryl-4,4-dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3-selenadiazoles which may lead to compounds with better a pharmacological profile than standard drugs and serve as templates for the construction of better drugs to fight bacterial and fungal infections.

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