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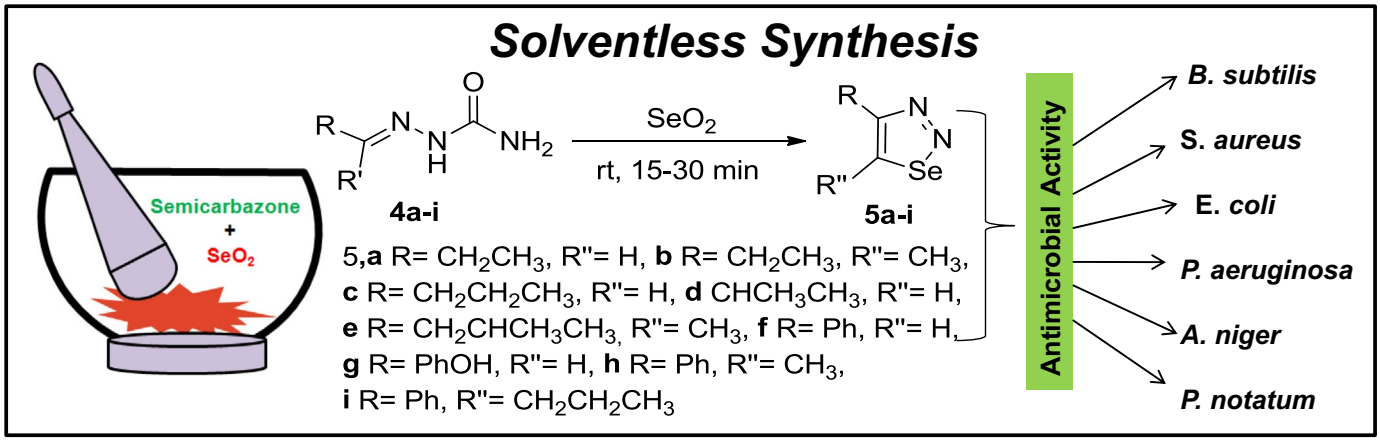

ORGANIC CHEMISTRY | RESEARCH ARTICLE

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Solventless synthesis of new 4,5-disubstituted 1,2,3-selenadiazole derivatives and their antimicrobial studies

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Abstract: Two novel, namely 5-Phenyl-4-methyl-1, 2, 3-selenadiazole **(5h)** and 4-Phenyl-5-propyl-1, 2, 3-selenadiazole **(5i)** along with several other aliphatic and aromatic series of 1,2,3-selenadiazoles were synthesized at room temperature in one step under solventless conditions from the corresponding semicarbazones. All compounds were thoroughly characterized by various spectroscopic tools. The synthesized new and reported 1,2,3-selenadiazoles were found active against bacterial as well as fungal stains when screened for their antimicrobial activity against various pathogenic bacteria and fungi using agar disc diffusion as well as agar well diffusion method. Almost all selenadiazoles showed better antibacterial properties in comparison to established antibiotics like tetracycline. 4-ethyl-5-methyl-1,2,3-selenadiazole showed higher antimicrobial activity amongst the tested selenadiazoles.

Subjects: Biochemistry; Chemical Spectroscopy; Organic Chemistry

Keywords: organoselenium compounds; selenadiazoles; semicarbazones; solventless synthesis; antimicrobial studies

Pawan K. Khanna

ABOUT THE AUTHOR

Pawan K. Khanna, the corresponding author, completed his PhD in Oganometallic Chemistry of Se & Te from IIT-Bombay in 1989–90. Subsequently he did postdoctoral research with Chris Morely at the Queens' University of Belfast and University of Wales at Swansea (UK). He worked in C-MET, Pune from 1993 to 1995. He was awarded the BOYSCAST fellowship of Govt of India during 1998–99 to work with David Cole-Hamilton at the Univesity of St. Andrews, Scotland. He moved to his current position of professor and head of Department of Applied Chemistry at Defence Institute of Advanced Technology (DIAT) in 2011 where he also served as dean of academics during 2011–2013. He has published over 150 research papers. *He was awarded MRSI medal in 2010 and Researcher of the Year award at DIAT in 2014.* Aditi Jadhav, Vaishali Dhanwe, Prasad Joshi are students of Pawan Khanna and are co-authors of the article. They are all developing organic and nanochemistry expertise.

PUBLIC INTEREST STATEMENT

This paper presents some novel compounds along with different series of heterocyclic organoselenium compounds i.e. 1, 2, 3-selenadiazoles synthesized at room temperature under solventless condition from corresponding semicarbazones and SeO_2. These one-step reaction methods are instant, environment-friendly, and convenient to work with. All compounds presented, are thoroughly characterized using different spectroscopic tools. The 1,2,3-selenadizoles are organoselenium compounds having many applications; which are useful as precursors for material chemistry and nanotechnology for the synthesis of various types of metal selenide nanoparticles. 1,2,3-selenadiazoles are biologically active compounds.

1. Introduction

The current interest in the chemistry of 1,2,3-selenadiazoles is mainly due to their chemical reactivity owing to their soft transformations upon thermolysis (Jadhav, Dhanwe, Joshi, & Khanna, 2015; Junling et al., 2004) and or photolysis that derive free selenium via elimination of a nitrogen molecule leading to formation of alkynes or new heterocycles (Jadhav, Dhanwe, et al., 2015; Meier & Voigt, 1972; Regitz & Krill, 1996; Jadhav & Khanna, 2015). Such new transformations make selenadiazoles and the end compounds thereof useful in pharmaceutical chemistry as well as precursors for coordination (Zhan, Liu, Fang, Pannecouque, & Clercq, 2009; Cervantes-Lee et al., 1998; Morley & Vaughan, 1993; Ford, Khanna, Morley & Vaira, 1999; Khanna & Morley, 1993) and materials chemistry including nanotechnology. (Khanna, 2005; Khanna, Gorte, & Morley, 2003; Khanna et al., 2009; Bhanoth, More, Jadhav, & Khanna, 2014; Jadhav, More, & Khanna, 2015).

The scope of 1,2,3-selenadiazole in pharmaceutical chemistry has widened due to resistance of micro-organisms against chemotherapeutic agents allowing infectious disease to become the second leading cause of death worldwide. Due to fast mutation process, many antibiotics become ineffective against the bacteria. As a result, bacterial resistance against antibiotic treatment is a common phenomenon. 1,2,3-selenadiazoles, in addition to their high-tech applications, have also been extensively studied for their pharmaceutical applications e.g. cytotoxicity and other biological activities. (Al-Smadi & Al-Momani, 2008; Pawar, Burungale, & Karale, 2009; Jalilian, Sattari, Bineshmarvasti, Daneshtalab, & Shafiee, 2003; El-Desoky, Badria, Abozeid, Kandeel, & Abdel-Rahman, 2013; Zhan et al., 2009; Xiao-Chun et al., 2012; Patil, Badami, & Puranik, 1994; Padmavathi, Sumathi, & Padmaja, 2002). Substituted 1,2,3-selenadiazoles and their derivatives have shown excellent antibacterial (Al-Smadi & Al-Momani, 2008; Pawar et al., 2009) antifungal (Jalilian et al., 2003), antitumor (El-Desoky et al., 2013; Xiao-Chun et al., 2012), and antiHIV properties (Zhan et al., 2009). Some of the 1,2,3-selenadiazole derivatives show antihaemostatic (Patil et al., 1994) and insecticidal activities (Padmavathi et al., 2002). Specially it is worth mentioning that thioacetanilides derivatives of 1,2,3-selenadiazoles showed antiHIV activity against HIV-I in MT-4 cells (Zhan et al., 2009). Antifungal study of 1,2,3-selenadiazoles e.g. sulphmoyl derivatives of 4,5-dihydronaphtho[1,2-d][1,2,3]selenadiazoles showed significant activity against *Cryptococcus neoformans*. Multiarm derivatives of 1,2,3-selenadiazoles were found highly active against *E. coli*, *S. aureus*, and *P. aurogenosa* bacteria (Al-Smadi & Al-Momani, 2008). Human melanoma cells (A375) growth was successfully inhibited by selenadiazole derivative i.e. 5-amino[1,2,5]selenadiazolo[3,4-*d*]pyrimidin-7-ol (El-Desoky et al., 2013). There are large number of such compounds useful as antimicrobial agents (Al-Smadi & Al-Momani, 2008; Pawar et al., 2009; Jalilian et al., 2003). Hence the researchers are continuously in the hunt for new molecules for controlling the bacterial infection timely and more effectively.

In view of excellent materials and biological applications of 1,2,3-selenadiazoles, it is warranted that meaningful studies should be conducted on such molecules to further enrich the knowledge bank so that their utility becomes more relevant. In order to tackle this issue, new 1,2,3-selenadiazole are required to be explored by conventional as well as non-conventional methods. We have recently reported solventless synthesis of cycloalkeno-1,2,3-selenadiazoles and tested their behavior towards several human pathogens (Jadhav, Dhanwe, et al., 2015). In our previous studies, a series of cyclic aliphatic 1,2,3-selenadiazoles were, for the first ever time, tested for their antibacterial activity and it was found that they act rather efficiently against number of microbes. To extend the feasibility of solventless synthesis and the effect of organic functionality via substitutions at 4 and 5 positions in the selenadiazole moiety on their antimicrobial activity, we herein report the synthesis of acyclic aliphatic and aromatic acetophenone derivatives of 1,2,3-selenadiazoles. Traditionally, 1,2,3-selandiazoles have been synthesized from the corresponding semicarbazones via ring closure due to mild oxidation of semicarbazones by selenium dioxide (selenious acid)(Regitz & Krill, 1996; bLabanauskas, Dudutiene, Matulis, & Urbelis, 2009; Lalezari, Shafiee, & Yalpani, 1971). Often the synthesis is based on solution method and except our last report (Jadhav, More, et al., 2015), there has not been any report described using solventless conditions for the preparation of 1,2,3-selenadiazoles. However, the solventless conditions have been occasionally mentioned for other types of

selenadiazoles. (Junling et al., 2004). Photochemical sensitivity of reaction and the product alike, coupled with large solvent requirement and extended work-up process, warrants alternative approach to avoid pre-degradation of the compounds. Among the studied compounds, 5-Phenyl-4-methyl-1, 2, 3-selenadiazole **(5h)** and 4-Phenyl-5-propyl-1, 2, 3-selenadiazole **(5i)** have not been reported earlier. This article therefore deals with the two new selenadiazoles along with several other such compounds (**5a**-**f**) which have not been reported by solvelentless method. Additionally, their antibacterial properties against the chosen microbes are studied in the current work.

2. Experimental

2.1. Chemicals and methods

All chemicals and solvents (reagent or analytical grade) were purchased from Sigma–Aldrich Company and Merck India Ltd. and were used as received. The UV–visible spectra were recorded qualitatively at room temperature in the range of 200–800 nm using Analytik Jena SPECORD 210 PLUS UV spectrophotometer. FTIR spectra were recorded at room temperature in the range of 4000–800 cm^{-1} using FTIR Perkin Elmer spectrum two spectrometer. ^{1}H and ^{13}C NMR spectra (300 and 75 MHz, respectively) recorded on a Bruker DRX-300 instrument in $CDCl_3$, and the chemical shifts were reported relative to TMS as an internal standard. The high-resolution mass spectra were recorded on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF (LC/MS) spectrometer with electron spray ionization. The melting points were determined in open capillaries. The progress of reactions was monitored by TLC on Merck silica gel 60 F-254 aluminum sheets, eluent EtOAc, visualization UV light.

2.2. Synthesis

2-butanone semicarbazone (4a). The semicarbazone derivatives were synthesized using reported procedure (Al-Smadi & Ratrout, 2004). Yield 18.9 g (72%), white crystals, R_f 0.58, mp 132–134°C (EtOH); Reported 144°C (Ibrahim & Al-Difar, 2011). UV spectrum (EtOH), λ_{max} (nm): 273. IR spectrum, ν (cm^{-1}):3473 (secondary N–H), 3190 (amide N–H), 1684 (C=O), 1587 (C = N), 1111 (NC=O), 2888 (C–H). ^{1}H NMR spectrum, δ (ppm): 1.06–1.11 (3H, m, CH_3); 1.84 (3H, s, CH_3); 2.22–2.29 (2H, m, CH_2); 6.06 (2H, s, NH_2); 8.46 (1H, s, NH).^{13}C NMR spectrum, δ (ppm): 10.51 (CH_3); 15.22 (CH_3); 33.82 (CH_2); 151.69 (C = N); 158.36 (C=O). Found, *m/z*: 130.0997 $[M]^+$. $C_5H_{12}N_3O$. Calculated, *m/z*: 130.0995

3-pentanone semicarbazone (4b) was synthesized analogously to compound **4a** from 3-pentanone. Yield 21.20 g (85%), white crystals, R_f 0.54, mp 102–105°C (EtOH) Reported 113°C (Ibrahim & Al-Difar, 2011). UV spectrum (EtOH), λ_{max} (nm): 267. IR spectrum, ν (cm^{-1}): 3446 (secondary N–H), 3234 (amide N–H), 1673 (C=O), 1573 (C = N), 1112 (NC=O), 2955 (C–H). ^{1}H NMR spectrum, δ (ppm): 1.06–1.10 (6H, m, $2CH_3$); 2.22–2.29 (4H, m, $2CH_2$); 6.00 (2H, s, NH_2); 8.74 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 9.60 (CH_3); 10.47 (CH_3); 22.39 (CH_2); 29.29 (CH_2); 155.95 (C = N); 158.86 (C=O). Found, *m/z*: 144.1131 $[M + H]^+$. $C_6H_{14}N_3O$. Calculated, *m/z*: 144.1136.

2-pentanone semicarbazone (4c) was synthesized analogously to compound **4a** from 2-pentanone. Yield 22.44 g (90%), white crystals, R_f 0.66, mp 106–108°C (EtOH). UV spectrum (EtOH), λ_{max} (nm): 257. IR spectrum, ν (cm^{-1}): 3472 (secondary N–H), 3219 (amide N–H), 1676 (C=O), 1590 (C = N), 1130 (NC=O), 2962 (C–H). ^{1}H NMR spectrum, δ (ppm): 0.90–0.95 (3H, m, CH_3); 1.49–1.64 (2H, m, CH_2), 1.84 (3H, m, CH_3), 2.17–2.22 (2H, m, CH_2); 5.94 (2H, br. s, NH_2); 8.69 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 16.5 (CH_3); 20.21 (CH_2); 33.45 (CH_2); 19.45 (CH_3); 150.00 (C = N); 158.12 (C=O). Found, *m/z*: 144.1137 $[M + H]^+$. $C_6H_{14}N_3O$. Calculated, *m/z*: 144.1136

Isopropyl methyl semicarbazone (4d) was synthesized analogously to compound **4a** from 2-butanone. Yield 19.45 g (78%), white crystals, R_f 0.60, mp 110–115°C (EtOH). UV spectrum (EtOH), λ_{max} (nm): 262. IR spectrum, ν (cm^{-1}): 3472 (secondary N–H), 3179 (amide N–H), 1667 (C=O), 1574 (C = N), 1127 (NC=O), 2877 (C–H). ^{1}H NMR spectrum, δ (ppm): 1.06–1.11 (6H, m, $2CH_3$); 1.84 (3H, S, CH_3); 2.21–2.32 (1H, m, CH); 6.18 (2H, s, NH_2); 8.35 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 18.01 ($2CH_3$); 22.23

(CH_3); 38.01 (CH); 148.05 (C = N); 158.41 (C=O). Found, *m/z*: 144.1132 $[M + H]^+$. $C_6H_{14}N_3O$. Calculated, *m/z*: 144.1136.

Isobutyl methyl semicarbazone (4e) was synthesized analogously to compound **4a** from isobutyl methyl ketone. Yield 14.54 g (61.78%), white crystals, R_f 0.56, mp 130–135°C (EtOH). UV spectrum (EtOH), λ_{max} (nm): 259. IR spectrum, ν (cm^{-1}): 3424 (secondary N–H), 324 (amide N–H), 1675 (C=O), 1537 (C = N), 1134 (NC=O), 2871 (C–H). ^{1}H NMR spectrum, δ (ppm): 0.90–0.95 (6H, m, CH_3); 1.49–1.61 (1H, m, CH); 1.84 (3H, s, CH_3); 2.17–2.22 (2H, m, CH_2); 6.04 (2H, s, NH_2); 8.68 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 18.23 ($2CH_3$); 22.54 (CH_2); 38.21 (CH); 20.12 (CH_3); 150.11 (C = N); 157.31 (C=O). Found, *m/z*: 158.1302 $[M + H]^+$. $C_7H_{16}N_3O$. Calculated, *m/z*: 158.1300.

Acetophnone semicarbazone (4f) was synthesized analogously to compound **4a** from acetophenone. Yield 18.14 g (82%), (Al-Smadi & Ratrout, 2004)

4-hydroxy acetophenone semicarbazone (4g) was synthesized analogously to compound **4a** from 4-hydroxy acetophenone. Yield 14.9 g (70%), (Al-Smadi & Ratrout, 2004)

Valerophenone semicarbazone (4h) was synthesized analogously to compound **3a** from 2-butanone. Yield 16.3 g (82%), white crystals, R_f 0.58, mp 163–165°C (EtOH). UV spectrum (EtOH), λ_{max} (nm): 270. IR spectrum, ν, cm^{-1}: 3453 (secondary N–H), 3188 (amide N–H), 3135 (Ar. H) 1678 (C=O), 1602 (Ar. C=C), 1575 (C = N), 1175 (NC=O), 2975 (C–H). ^{1}H NMR spectrum, δ (ppm): 0.91–0.93 (3H, m, CH_3); 1.21–1.26 (2H, m, CH_2); 1.58–1.64. (2H, m, CH_2); 2.70–2.73(2H, m, CH_2); 7.43–7.47(2H, m, Ar.CH); 7.72–7.75(3H, m, Ar.CH); 6.21(2H, s, NH_2); 8.90 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 10.41 (CH_3); 27.2 (CH_2); 28.3 (CH_2); 29.78 (CH_2); 123.27, 127.03, 140.80 (Ar Cs); 144.54 (C = N); 158.65 (C=O). Found, *m/z*: 220.1469 $[M + H]^+$. $C_{12}H_{18}N_3O$. Calculated, *m/z*: 220.1467.

Propeophenone semicarbazone (4i) was synthesized analogously to compound **4a** from propeophenone. Yield 11 g (77.19%), white crystals, R_f 0.55, mp 165–168°C (EtOH). UV spectrum (EtOH), λ_{max} (nm): 260. IR spectrum, ν (cm^{-1}): 3451 (secondary N–H), 3199 (amide N–H), 3140 (Ar. H) 1689 (C=O), 1602 (Ar. C=C), 1575 (C = N), 1198 (NC=O), 2973 (C–H). ^{1}H NMR spectrum, δ (ppm): 1.18–1.22 (3H, m, CH_3); 2.69–2.72 (2H, m, CH_2); 7.48–7.52 (2H, m, Ar.CH); 7.70–7.74 (3H, m, Ar.CH); 6.2 (2H, s, NH_2); 8.60 (1H, s, NH). ^{13}C NMR spectrum, δ (ppm): 10.23 (CH_3); 20.12 (CH_2); 126.34, 128.43, 130.42 (ArCs); 150.16 (C = N); 158.40 (C=O). Found, *m/z*: 192.1134 $[M + H]^+$. $C_{10}H_{14}N_3O$. Calculated, *m/z*: 192.1132.

4-ethyl-1,2,3-selenadiazole (5a) (General Method). 2-butanone semicarbazone (**4a**) (5g, 0.029 mol) and selenium dioxide (3.2 g, 0.029 mol) were ground together in a mortar pestle at room temperature for around 20 min. The process was monitored by TLC using hexane–AcOEt, 7:3, as solvent system. The crude product was dissolved in 100 ml toluene and filtered. The filtrate was evaporated using a rotary evaporator. The product was purified by column chromatography on silica gel (60–120 mesh), using petroleum ether (bp 60–80°C)—toluene, 7:3, as eluent. Yellow liquid product was collected as a final product which is characterized by UV–visible, FTIR, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. Yield 3.12 g (50%), UV spectrum (toluene), λ_{max} (nm): 341. R_f 0. 67. IR spectrum, ν (cm^{-1}): 2921–2847 (C–H), 1620 (C=C), 1454 (C–H), 1302 (C–N). ^{1}H NMR spectrum, δ (ppm), *J*(Hz): 1.45 (3H, *J* = *5*, t, CH_3); 3.27 (2H, m, CH_2); 8.86 (1H, s, selenadiazole ring H). ^{13}C NMR spectrum, δ (ppm): 14.13 (CH_3); 29.99 (CH_2); 137.06 (C=C–N); 165.26 (C=C–Se). Found, *m/z:* 162.9776 $[M + H]^+$. $C_4H_7N_2Se$. Calculated, *m/z*: 162.9773.

4-ethyl-5-methyl-1, 2, 3-selenadiazole (5b) was synthesized analogously to compound **5a**. Yield 3.11 g (51%), yellow liquid, R_f 0.70. UV spectrum (toluene), λ_{max} (nm): 327. IR spectrum, ν (cm^{-1}): 2923–2870 (C–H), 1585 (C=C), 1445 (C–H δ), 1291 (C–N s). ^{1}H NMR spectrum, δ (ppm), *J* (Hz): 0.85–0.87 (3H, m, *J* = 5.0, CH_3); 2.04–2.07 (2H, m, *J* = 5.0, CH_2); 1.80 (3H, s, CH_3); ^{13}C NMR spectrum, δ (ppm): 16.16 (CH_3-CH2); 22.07 (CH_2); 17.86 (CH_3); 153.35 (C=C–N); 161.06 (C=C–Se). Found, *m/z*: 176.9927 $[M + H]^+$. $C_5H_9N_2Se$. Calculated, *m/z*: 176.9926.

4-propyl-1, 2, 3-selenadiazole (5c) was synthesized analogously to compound **5a**. Yield 2.9 g (48%), yellow liquid, R_f 0.78. UV spectrum (toluene), λ_{max} (nm): 341. IR spectrum, ν (cm^{-1}): 2917–2850 (C–-H), 1645 (C=C), 1445 (C–H), 1300 (C–N). ^{1}H NMR spectrum, δ (ppm), *J* (Hz): 0.87 (3H, t, *J* = 5.0, CH_3); 1.71–1.77 (2H, m, *J* = 5, CH_2); 3.06 (2H, t, *J* = 5, CH_2); 8.80 (1H, s, selenadiazole ring H). ^{13}C NMR spectrum, δ (ppm): 13.32 (CH_3); 22.71 (CH_2-CH_3); 31.06 (CH_2-CH_2); 137.59 (C=C–N); 163.14 (C=C–Se). Found, *m/z*: 176.9928 $[M + H]^+$. $C_5H_9N_2Se$. Calculated, *m/z*: 176.9926.

4-iso-propyl-1, 2, 3-selenadiazole (5d) was synthesized analogously to compound **5a**. Yield 3.29 g (54%), yellow liquid, R_f 0.65. UV spectrum, λ_{max} (nm): 322. IR spectrum, ν, cm^{-1}: 2923–2869 (C–H), 1620 (C=C), 1462 (C–H), 1300 (C–N). ^{1}H NMR spectrum, δ (ppm), *J* (Hz): 1.35 (6H, m, CH_3); 3.45–3.53 (H, m, CH); (1H, S, heterocyclic ring H). ^{13}C NMR spectrum, δ (ppm): 22.58 (CH_3-CH-CH_3); 29.42 (CH); 135.87 (C=C–N); 169.65 (C=C–Se). Found, *m/z*: 176.9930 $[M + H]^+$. $C_5H_9N_2Se$. Calculated *m/z*: 176.9929.

4-isobutyl-1, 2, 3-selenadiazole (5e) was synthesized analogously to compound **5a**. Yield 3.12 g (52%), yellow liquid, R_f 0.78. UV spectrum (toluene), λ_{max} (nm): 325. IR spectrum, ν (cm^{-1}): 2923–2867 (C–H), 1633 (C=C), 1462 (C–H), 1292 (C–N). ^{1}H NMR spectrum, δ (ppm), *J* (Hz): 0.80 (6H, t, *J* = 5, CH_3); 1.99–2.06 (H, m, CH); 2.90 (2H, t, *J* = 5, CH_2); 8.71 (1H, s, selenadiazole ring H). ^{13}C NMR spectrum, δ (ppm): 21.75 (CH_3-CH-CH_3); 28.66 (CH); 37.86 (CH_2); 138.24 (C=C–N); 161.98 (C=C–Se). Found, *m/z*: 191.0089 $[M + H]^+$. $C_6H_{11}N_2Se$. Calculated, *m/z*: 191.0087.

4-(4-hydroxyphenyl) -1, 2, 3-selenadiazole (5f) was synthesized analogously to compound **5a**. Yield 2.61 g (45%), reddish solid, R_f 0.42. (Al-Smadi & Ratrout, 2004)

5-phenyl-1, 2, 3-selenadiazole (5g) was synthesized analogously to compound **5a**. Yield 2.81 g (48%), reddish solid, R_f 0.57. (Al-Smadi & Ratrout, 2004)

4-phenyl-5-propyl-1, 2, 3-selenadiazole (5h) was synthesized analogously to compound **5a**. Yield 3.3 g (48%), yellow viscous solid, R_f 0.62. UV spectrum (toluene), λ_{max} (nm): 327. IR spectrum, ν (cm^{-1}): 3027–3031(Ar C–H), 2853–2927 (C–H), 1600 (Ar C=C), 1660 (C=C), 1449 (C–H), 1227 (C–N). ^{1}H NMR spectrum, δ (ppm): 7.45–7.52 (3H, m, Ar CH); 7.68–7.70 (2H, m, Ar CH); 0.99–1.02 (3H, m, CH_3); 1.75–1.80 (2H, m, CH_2); 3.05–3.09 (2H, m, CH_2);. ^{13}C NMR spectrum, δ (ppm): 13.91 (CH3- CH_2- CH_2); 27.87 (CH_3- CH2- CH_2); 31.00 (CH_3- CH_2- CH2); 127.91, 128.35, 128.58, 129.41 (Ar Cs); 132.17 (C=C–N); 162.45 (C=C–Se). Found, *m/z*: 253.0244 $[M + H]^+$. $C_{11}H_{13}N_2Se$. Calculated, *m/z*: 253.0243.

5-phenyl-4-methyl-1, 2, 3-selenadiazole (5i) was synthesized analogously to compound **5a**. Yield 2.07 g (45%), pinkish solid, R_f 0.45. mp 130–132°C. UV spectrum (toluene), λ_{max} (nm): 300. IR spectrum, ν (cm^{-1}): 3078–2993 (Ar C–H), 2915 (C–H), 1595 (Ar C=C), 1658 (C=C), 1445 (C–H), 1285 (C–N). ^{1}H NMR spectrum, δ (ppm) : 2.59 (3H, s CH_3), 6.94–6.99 (3H, m, Ar CH); 7.87–7.90 (2H, m, Ar CH). ^{13}C NMR spectrum, δ (ppm): 31.58 (CH_3); 127.76, 128.35, 129.15, 132.39 (Ar Cs); 136.66 (C=C–N); 156.09 (C=C–Se). Found, *m/z*: 224.9934 $[M + H]^+$. $C_9H_9N_2Se$. Calculated, *m/z*: 224.9930.

2.3. Antimicrobial study

The antimicrobial study was carried out at Kulkarni Laboratory and Quality Management Services at Pune, India. Microbial strains used in the study were clinical isolates of bacteria *Staphylococcus aureus*, *Escherechia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa*, as well as fungi *Aspergillus niger* and *Penicillium notatum*. Muller Hinton agar media (gm/litre) was used for media preparation. For 1000 ml Muller Hinton agar preparation peptone 5 g, sodium chloride 8 gm, beef infusion 3 gm, and agar 16 gm were weighed and dissolved in 1000 ml of distilled water and maintained pH 7.3–7.4 which was sterilized by autoclaving at 121°C for 15 min at 15 psi pressure.

All synthesized compounds **5a-i**, were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria at concentration 0.0049 g/ml using two different methods involving agar disc diffusion and agar well method with Muller Hinton agar media (Table 1).The

Table 1. Sensitivity of human pathogenic microbes to 1,2,3-selenadiazoles 5a–i using the agar disc and agar well diffusion method

Sample codes	Conc. (g/ml)	Diameter of zone of inhibition (mm)									
		S. aureus		*P. aeruginosa*		*E. coli*		*B. subtillis*		*A. nigar*	*P. notatum*
		D.D.[1]	W.D.[2]	D.D.	WD	D.D.	W.D.	D.D.	W.D.	W.D.	W.D.
5a	0.0049	17	22	12	20	12	15	20	30	20	23
5b	0.0049	16	23	15	22	13	15	23	27	22	24
5c	0.0049	17	21	12	20	17	18	17	30	21	23
5d	0.0049	15	20	11	15	10	17	20	25	18	23
5e	0.0049	14	17	11	15	9	16	17	22	17	20
5f	0.0049	15	18	12	17	-	15	16	20	10	15
5g	0.0049	11	17	11	12	12	15	15	17	10	14
5h	0.0049	12	16	10	16	10	18	11	17	9	10
5i	0.0049	10	15	10	15	10	17	10	17	8	9
Tetracycline		20	12	12	23	–	–				

[1]D. D.: Disc diffusion method.

[2]W. D.: Well diffusion method; (–) not done.

selected bacterial suspension was spread on the surface of Muller Hinton agar plates respectively. In case of agar disc diffusion method, the synthesized compounds were impregnated on Whatman No. 1 filter paper disc (6 mm diameter) at a concentration of 0.0049 g/ml. Each disc is coded with the name of the agent. Discs were placed on solidified media and allowed to diffuse for 5 min; the plates were kept for incubation at 37°C for 24 h for bacteria. Dimethylsulfoxide (DMSO) was used as the control. At the end of incubation, antibacterial activity was determined by measuring zone of inhibition in mm around each of the disc and compared with standard DMSO.

To check the antimicrobial activity of the samples against test organisms by well diffusion method, freshly prepared nutrient agar was seeded with 1% inoculums of each test organism. The 8-mm diameter wells were cut with the help of cork borer. Each well was then filled with sample (approximately 100 µl). All the plates were incubated at 37°C for 24 h. The zone of inhibition around each disc was measured after completion of incubation time.

Antifungal activity of the samples: Similar procedure was used to check the antifungal activity of the test samples. Fungal strains used for these studies are *Aspergillus niger* and *Penicillium notatum*. Potato Dextrose agar was used to check the activity. The fungal spores was dispensed in sterile saline with 1% Tween 80 and seeded to PDA media. The 8-mm diameter wells were cut with the help of cork borer. Each well was then filled with sample. All the plates were incubated at room temperature for five days. The zone of inhibition around each disc was measured after completion of incubation time.

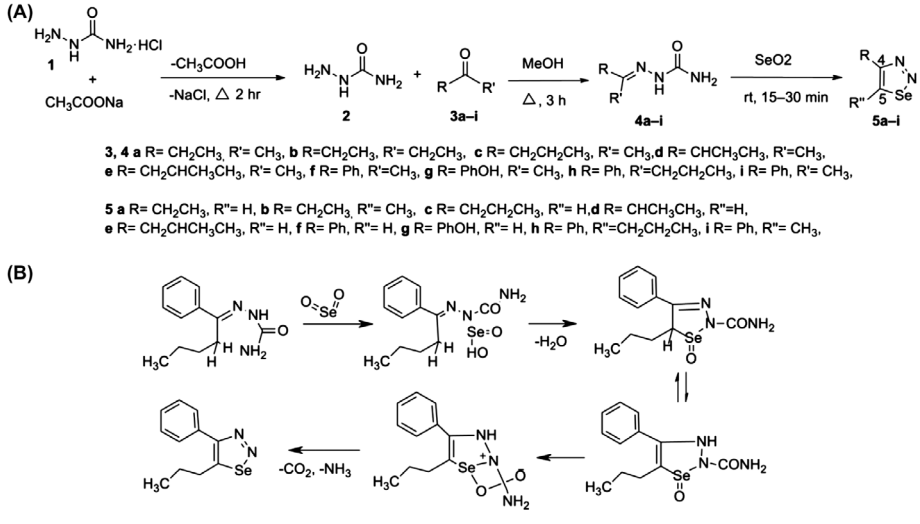
3. Results and discussion

In the current work, we present the synthesis of two novel 1,2,3-selenadiazoles (**5h,i**) and comparative study of antimicrobial behavior of different series of 1,2,3-selenadiazoles. The synthesized compounds were tested against two Gram-positive and Gram-negative bacteria as well as fungi species by two different methods of antimicrobial screening. We herein present a solventless method for preparation of 1,2,3-selenadiazoles from the respective semicarbazones. Semicarbazones **4a–i** can be easily synthesized by a reported procedure (Al-Smadi & Ratrout, 2004) from the respective ketones **3a–i** and semicarbazide hydrochloride **1**. We have earlier opined that a solventless cyclization

process is a rapid method in comparison to the solution chemistry and requires lesser time with reduced or negligible amount of solvent for the isolation of product. In our experiments, the solventless reaction of semicarbazones **4a–i** with selenium dioxide requires hand grinding only and could be completed within 30–60 min producing 1,2,3-selenadiazoles **5a–i** in moderate yields. Additionally, during synthesis it was observed that solventless method is more feasible for the synthesis of aliphatic derivatives of 1,2,3-selenadiazoles **5a-e** compared to aromatic derivatives **5f-i**. It is further noted that compounds **5f-i** need longer grinding (reaction) time with low yield compared to compounds **5a-e.**

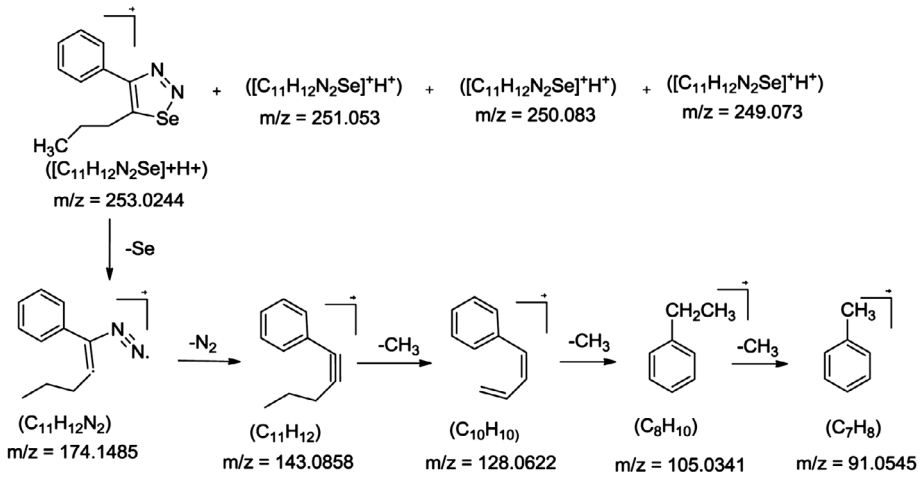
The structures of various semicarbazones **3a–i** and selenadiazoles **5a–i** were confirmed by UV–visible, FTIR, ^{1}H and ^{13}C NMR spectroscopy, and mass spectrometry. UV–visible spectra of 1,2,3-selenadiazoles **5a–i** showed absorption bands $\lambda_{(abs)}$ at ~300–350 nm due to π–π* electronic transition of C=C in conjugation with N = N in which the N and C are attached to the Se atom in heterocyclic ring. The longer wavelength absorption was observed due to extensive conjugation along with the presence of Se in heterocyclic ring.

FTIR spectra of compounds **5a–i** were recorded as KBr pellets. Figure SI 1 shows IR spectrum of 4-phenyl-5-propyl-1, 2, 3-selenadiazole. Generally, peaks at 2951–2848 cm^{-1} are due to C–H stretching mode of vibrations and at 1648–1627 cm^{-1} for C=C stretching mode of vibrations (due to Se-C=C–N moiety in 1,2,3-seleadiazoles).The IR transmission band at 1482–1436 cm^{-1} was assigned to C–H deformation mode vibrations, and the band at 1303–1286 cm^{-1} is assigned to C–N stretching mode of vibrations. Whereas, compounds having aromatic moieties showed additional bands at 3130–3080 cm^{-1} and 1580–1600 cm^{-1} which can be assigned to Ar C–H and C=C stretch, respectively. FTIR spectra show obvious variations in Ar C–H, C=C stretch along with other stretching modes of vibrations because of varying organic substituents at R and R' groups. The ^{1}H NMR spectra of 1,2,3-selenadiazoles **5a–i** in $CDCl_3$ showed different chemical shifts for CH, CH_2, and CH_3 protons in the range of δ 1.10–3.25 ppm for alkyl groups. For protons associated with the heterocyclic ring chemical shifts are observed in the range of δ 8.70–9.50 ppm. Similarly, compounds having aromatic moieties showed chemical shifts in the range of δ 6.90–8.3 ppm for aromatic ring protons. Likewise, the ^{13}C NMR spectrum of 1,2,3-selenadiazoles **5a–i** showed the expected number of signals due to different carbon atoms in the molecules. Chemical shift at around δ 130–137 ppm and δ 157–165 ppm are assigned to (C=C–N) and (C=C–Se) heterocyclic ring carbon atoms, respectively. For typical understanding the ^{1}H NMR and ^{13}C NMR spectrum of 4-phenyl-5-propyl-1, 2, 3-selenadiazole is shown in Figure SI2 and 3. Mass spectra of 1, 2, 3-selenadiazoles showed peaks with a set of isotopic components, characteristics of the presence of selenium which has 8 naturally occurring isotopes with atomic mass 72–82 out of which only 6 isotopes are stable. The *m/z* value of all the compounds



Scheme 1. (A) Synthesis of semicarbazones and their respective 1,2,3-selenadiazoles, (B) typical mechanism for synthesis of 4-phenyl-5-propyl-1, 2, 3-selenadiazole.

Scheme 2. Mass fragmentation pattern of 4-Phenyl-5-propyl-1, 2, 3-selenadiazole (5h).

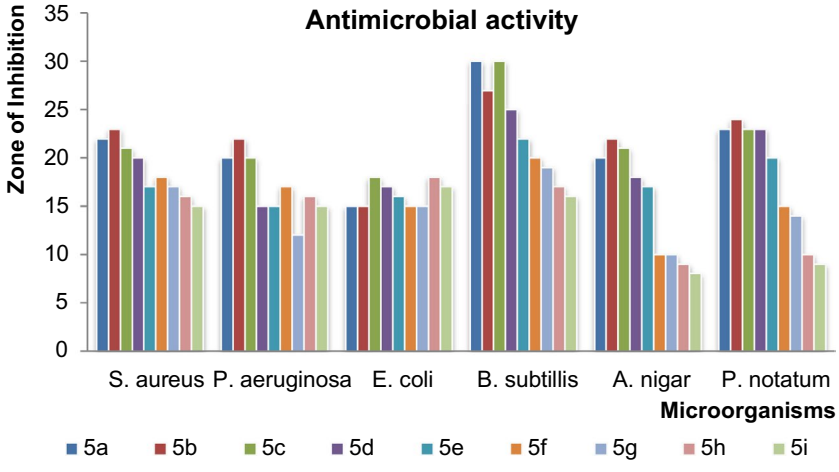


corresponded to the respective protonated molecular ions. To study the fragmentation pattern through MS–MS, analysis of some samples were carried out. The mass fragmentation pattern of 4-Phenyl-5-propyl-1, 2, 3-selenadiazole is shown in scheme 2 (Figure SI 4a,b). In a typical fragmentation analysis, molecular ion peak undergoes initial breakdown by loss of selenium followed by elimination of a nitrogen molecule to form asymmetric alkynes. Alkyne so generated may further dissociate stepwise by loss of a methyl group to eventually result in the formation of toluene molecule.

3.1. Antimicrobial studies

The activity of synthesized selenadiazoles **5a–i** was tested against some human pathogenic microbes. For studying their activity, two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtillis*) species were selected. For more authentication antibacterial activity of compounds were tested by two different methods i.e. agar disc diffusion method and agar well diffusion method. All the compounds described in this text were also screened for antifungal activity against *Aspergillus niger* and *Penicillium notatum*. From the results obtained by these methods, it was found that agar well method compared to agar disc diffusion method gives better results and thus can be considered more suitable for selenadiazoles. Encouraged with the suitability of agar well method for antibacterial screening, antifungal activity testing was also performed following the same method. Some of the tested compounds were highly active even at concentrations as low as 4.9 mg/ml (Table 1, Figure 1). For example, compound **5a** showed good inhibition against the highly resistant *Pseudomonas aeruginosa.* Generally, the

Figure 1. Sensitivity of 1,2,3-selenadiazoles 5a–i against human pathogenic microbes.



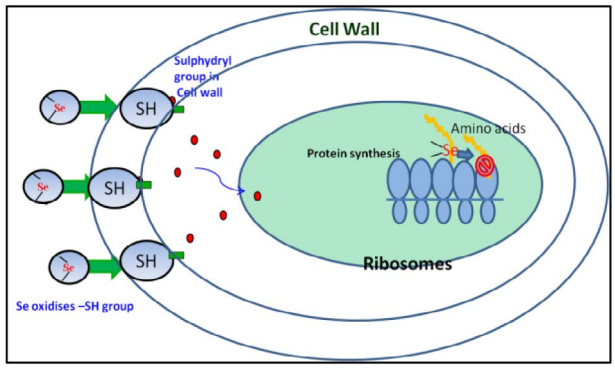


Figure 2. Proposed mechanism of bacterial cell growth inhibition by 1,2,3-selenadiazoles.

extracts of all selenadiazoles **5a**–**i** in dimethyl sulfoxide (DMSO) were active against all the tested pathogens, in the range of 8–25 mm diameter inhibition zone. DMSO used as control which showed no activity against any of the tested pathogens. On the basis of the presented data, it can be concluded that the tested 1,2,3- selenadiazoles **5a**–**i** possess good antimicrobial properties compared to tested antibiotic drugs such as tetracycline. Tetracycline is well-known antibiotic for the inhibition of microbial cell growth as it suppresses protein synthesis. Tetracycline showed zone of inhibition against tested bacteria in the range of (20–23 mm) where many of the selenadiazoles showed better zones inhibition than the drug. It is further observed that 1,2,3-selenadiazoles **5a**–**i** showed maximum activity against Gram-positive *Bacillus subtillis* and minimum activity against Gram-negative *E.Coli.* Amongst various selenadiazoles tested, compound **5b** showed maximum inhibition against all the pathogens. Selenadiazoles in which R and R' both groups are aliphatic showed better zone of inhibition in comparison to selenadiazoles in which R is an aromatic group. Within aliphatic series compounds, it was observed that compounds having branched chain alkyl groups showed lesser zone of inhibition compared to compounds having straight chain alkyl groups. The probable reason for variation in activity among selenadiazoles could be due to the variation in their stability and solubility. Since aliphatic series compounds are less stable, release of Se from such compounds is more efficient, thus making them more effective. However due to higher stability and less solubility aromatic series compounds in DMSO, they show marginally poor activity against the tested pathogens.

3.2. Mechanism of action

It has been reported that the cause of suppression of bacterial growth in presence of antibacterial agents could be due to several factors e.g. interference of compounds with cell wall synthesis, inhibition of protein synthesis by binding to various ribosomal subunits, suppression of nucleic acid synthesis, disturbances to metabolic pathway, and disruption of bacterial membrane structure. It is opined that selenadiazoles may show good antimicrobial activity due to the presence of diazole fragment along with selenium. There are a few selenium-containing organic compounds with a reported antibacterial activity (Radhakrishna et al., 2010). It can be postulated that selenium might partially replace sulfur in sulfur-containing amino acids present in the bacterial cells (Figure 2) and inhibit their growth due to toxicity of selenium compounds and metabolic disturbances to the microorganisms (Li, Liu, Wu, Liang, & Qu, 2002; Bemheim & Klein, 1941). In the present series of compounds, initial elimination of selenium from 1,2,3-selenadizoles may interact with microbes to alter their bioactivities. Such studies therefore, clearly indicate that selenium plays an important role for these compounds to enhance their antimicrobial activity.

4. Conclusions

In conclusion, synthesis and characterization of different series of other 1,2,3-selenadiazoles by solventless method are presented. Fragmentation pathway for some new molecules was ascertained by m/z spectroscopy. All the selenadiazoles were tested for their antimicrobial activity to highlight

that they showed excellent antimicrobial activity against wide range of bacteria and fungi. The instant formation of such organoselenium compounds will likely promote their application in pharmaceutical chemistry, biochemistry, microbiology.

Supplementary Material
Supplementary material for this article can be accessed here http://dx.doi.org/10.1080/23312009.2016.1144670.

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