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Synthesis, characterization and antibacterial activity of some new ferrocenyl selenazoles and 3,5-diferrocenyl-1,2,4-selenadiazole

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ABSTRACT

New ferrocenyl containing selenazole derivatives were synthesized from reactions of aryl selenocarboxamide (*i.e.* Ar–C=Se(NH_2); Ar=C_6H_5 (**1**), 4-Br-C_6H_4 (**2**), 4-PhC_6H_4 (**3**), 4-$CH_3OC_6H_4$ (**4**), 4-$CH_3SC_6H_4$ (**5**), 6-MeO–naphyl (**6**), 4-MeO–naphthyl (**7**), 4-$C_2H_5OC_6H_4$ (**8**), 3,4-$(CH_3O)_2C_6H_3$ (**9**), and 3,5-$(CH_3O)_2C_6H_3$ (**10**)) with (2-bromoacetyl)ferrocene. The structures of the new compounds were determined by elemental analyses, IR, ^1H and ^{13}C NMR and mass spectroscopic data.

Reaction of 1-cyanoferrocene with sodium hydrogen selenide (NaHSe) in methanol gave the new ferrocenyl selenocarboxamide (**11**) in 27% yield. Treatment of compound **11** with a catalytic amount of $Na_2[PdCl_4]$ gave 3,5-diferrocenyl-1,2,4-selenadiazole in 35% yield. Both compounds were characterized elemental analyses and spectroscopic techniques.

Compounds **1**–**10** and **12** were screened as antibacterial agents against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and showed promising properties.

Introduction

The interest in selenazoles has been growing during the last decades not only for their importance in synthetic chemistry only but also for their biological properties [1]. 1,3-Selenazoles were found to be of pharmacological importance due to their antibiotic and cancerostatic activity [2]. Selenazole heterocycles, namely C-glycosylselenazole (*selenafurin*), are being studied because of its anti-bacterial activities [2a] while 2-aminoselenazoles because of their superoxide anion-scavengers [3].

A number of synthetic routes have been developed for the synthesis of selenium-containing interesting heterocyclic compounds because of their unique reactivity [4,5]. It is worth noting that [1,2,3]-selenadiazole-4-yl-ferrocene, di-[1,2,3]-selenadiazole-4-yl-ferrocene and their sulfur analog were prepared from the reaction of ketones with semicarbazones or hydrazones [6a]. The synthesis and evaluation of ferrocenyl thiazole derivatives as anti-cancer agents have been reported [6b]. On the other hand, ferrocene and its derivatives have received considerable attention for their biological activity [7]. Ferrocifen which is a ferrocene derivative of tamoxifen was submitted to clinical trial as breast anti-cancer drug [8].

However, to the best of our knowledge, there is no report described the synthesis and evaluating biological activities of ferrocene derivatives that contains selenazoles or selenadiazoles. Thus, herein we described the synthesis and biological activities of some new ferrocenyl containing selenazole or selenadiazole moieties.

Results and discussion

Aryl selenocarboxamides were prepared by treatment of aryl-nitriles with NaHSe in ethanol according to a reported method [9], Scheme 1. All these compounds were obtained as yellow or orange solids and were characterized by their melting points, IR and ^1H NMR spectroscopic data, which agrees well with previously reported data [9,10].

(2-Bromoacetyl) ferrocene was prepared as a red needle in 35% yield by treatment of ferrocene with bromoacetyl bromide in presence of $AlCl_3$, Scheme 1.

Reaction of the primary aryl selenocarboxamides with (2-bromoacetyl) ferrocene gave the corresponding 2-diaryl-4-ferrocenyl-1,3-selenazoles (**1**–**10**) in fair to good yields (Experimental section, Scheme 1).

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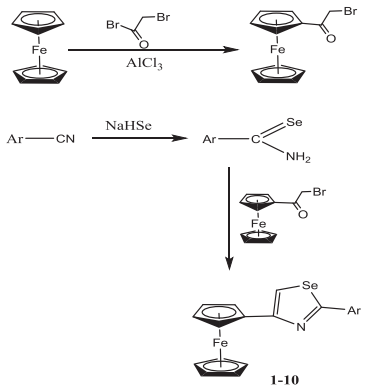


Ar = C_6H_5, 4-BrC_6H_4, 4-PhC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3SC_6H_4$, 6-CH_3O-Naphthyl, 4-CH_3O-Naphthyl, 4-$EtOC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$ and 3,5-$(CH_3O)_2C_6H_3$

Scheme 1. Methods of preparation of compounds **1**–**10**.

All 2-diaryl-4-ferrocenyl-1,3-selenazole derivatives (**1**–**10**) are red or orange solids with sharp melting point which are soluble in common organic solvents. The IR spectra of all compounds show an absorption band between 1580–1630 cm^{-1} due to ν(C=N) and an absorption band in range 595–560 cm^{-1} may assigned to ν(Se–C) [9,11,12]. The characteristic frequencies observed of the compounds **1**–**10** around 3081, 1442, 1105, 830, 503 and 482 cm^{-1} are attributed to the ferrocenyl moieties ν(C–H), ν(C–C), ν(C–H), ν(C–H) and ν(Fe-ring), respectively [12,13]. Furthermore, the (C–H) vibrations for the selenazole ring in compounds **1**–**10** is observed in the region 3070–3011 cm^{-1}, which is characteristic of heteroaromatic compounds [13].

^{1}H NMR spectra of compounds **1**–**10** were recorded in $CDCl_3$ and gave a further support for the formation of these compounds. The ^{1}H NMR spectra consist of, in addition to SCH_3, OCH_3 and OCH_2CH_3, low field signals of aryl protons at the range 6.98–8.89 ppm. The ^{1}H NMR spectra of compounds **1**–**10** exhibited triplet for substituted Cp ring around 4.92 and 4.78 ppm and a singlet for unsubstituted Cp ring around 4.23 ppm. Furthermore, all spectra showed one singlet signal downfield between 8.75 and 8.89 ppm due to the H-selenazole ring, which agrees well with the literature values [10].

^{13}C NMR data are in good agreement with the formulation of these compounds. In general, the ^{13}C NMR spectra of all compounds (**1**–**10**) showed the characteristic signals of the 1,3-selenazole ring skeleton carbons, signals for the carbons of the mono and unsubstituted cyclopentadienyl rings and signals for the aryl groups. For example, the ^{13}C spectrum of compound **5** shows signals at 75.1, 69.9, 68.8 and 68.6 ppm for the carbons of mono and unsubstituted cyclopentadienyl rings, and signals at 168.3, 163.8 and 121.2 ppm for C2, C4 and C5 for selenazole ring, respectively. Furthermore, signal at 17.2 ppm due to SCH_3 group was observed. All ^{13}C data are presented in the Experimental section.

The mass spectra of compounds **1**, **2**, **3**, **5**, **10** and **12** show the molecular ion with a correct isotope pattern for compounds containing selenium. The base peak of each spectrum was based on $ArCN^+$ which is corresponding to the loss of $FcC{=}CHSe^+$ ion. In general, the mass spectra of these compounds show the characteristic features of selenazole compounds and the exact fragmentation patterns. Furthermore, fragments at 186, 121 and 56 were observed in all spectra due to ferrocene moiety.

The synthetic method for 3,5-diferrocenyl-1,2,4-selenadiazole (**12**) based on the preparation of cyanoferrocene which was treated with NaHSe (prepared *in situ*) to afford the new ferrocenyl selenocarboxamide (**11**) in 27% yield as a red solid, Scheme 2.

The IR spectrum of compounds **11** showed the appearance of bands due to NH_2 asymmetrical and symmetrical stretching at 3314 and 3215 cm^{-1}, respectively. The spectrum showed strong band at 1623 cm^{-1} due to the deformation of N–H. Furthermore, the spectrum showed intense band at 620 cm^{-1} and a medium band at 380 cm^{-1} assigned to the C–Se stretching contribution [9,11,14].

^{1}H NMR spectrum of compound **11** showed two broad singlet signals at 9.45 and 10.34 ppm due to the –C(=Se)NH_2 group, which agrees well with the literature values [9,14]. The spectrum showed singlet signal at 4.18 ppm for unsubstituted cyclopentadienyl ring and two triplets at 4.62 and 4.42 ppm for monosubstituted cyclopentadienyl ring with the proper intensity ratio (Experimental section).

Compound **11** was treated with a catalytic amount of Na_2PdCl_4 to give the new 3,5-diferrocenyl-1,2,4-selenadiazole (**12**) as orange–red crystals in 35% yield, Scheme 2. The IR spectrum of **12** indicates clearly the absence of ν(NH_2) and ν(C=Se) and the appearance of medium band at 1680 cm^{-1} for ν(C=N) and at 515 cm^{-1} corresponding to ν(C–Se) [10–12].

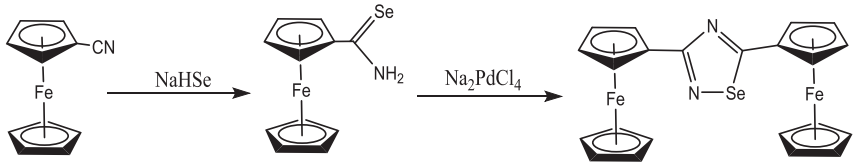
^{1}H NMR spectrum of compound **12** showed all the expected peaks with the proper intensity ratio, see Experimental section. ^{13}C NMR spectrum of compound **12** showed signals at 173.6 and 166.2 for C4 and C5 carbons of the selenadiazole ring with the expected signals for the carbons of mono and unsubstituted cyclopentadienyl rings, Experimental section.

Antibacterial activity

It is worth noting that ferrocenyl thiazole derivatives showed some degree of biological activity [15]. This prompted us to evaluate the antimicrobial activity of some synthesized compounds (*i.e.* compounds **1**–**10** and **12**) against different strains of bacteria.

The antimicrobial activity of tested compounds against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* is shown in Table 1.

From Table 1, it can be concluded that all the compounds have displayed some activity against bacteria. Compound **5** is highly active against *E. coli* which may due to the combined activity of sulfur and selenium in this compound. Compound **8** also showed good activity toward the three bacteria. This increase in activity may due to presence of ethoxy groups in this compound. Compounds **3**, **6** and **7** showed minimum activity against all strains. This may be attributed to the presence of a bulky naphthyl and phenyl



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Scheme 2. Methods of preparation of compounds **11**and **12**.

Table 1
Antibacterial activity expressed as inhibition diameter zone in millimeter (mm) of compounds **1**–**10** and **12** at 40 μg/ml.

Compounds	Zone of inhibition (mm)		
	S. aureus	*E. coli*	*P. aeruginosa*
1	17 ± 0.33	16 ± 0.33	17 ± 0.33
2	19 ± 0.33	20 ± 0.33	19 ± 0.33
3	16 ± 0.33	15 ± 0.33	15 ± 0.33
4	19 ± 0.33	20 ± 0.33	19 ± 0.33
5	21 ± 0.33	23 ± 0.33	19 ± 0.33
6	15 ± 0.33	16 ± 0.33	13 ± 0.33
7	16 ± 0.33	15 ± 0.33	13 ± 0.33
8	19 ± 0.33	20 ± 0.33	20 ± 0.33
9	18 ± 0.33	19 ± 0.33	18 ± 0.33
10	20 ± 0.33	18 ± 0.33	17 ± 0.33
12	19 ± 0.33	21 ± 0.33	20 ± 0.33
Chloramphenicol	35 ± 0.01	33 ± 0.00	32 ± 0.33

All the values are expressed as mean ± SEM triplicate.

Table 2
Antibacterial activity (MIC μg/ml) of compounds **1**–**10** and **12**.

Compounds	*S. aureus*	*E. coli*	*P. aeruginosa*
1	20	5	5
2	30	5	5
3	30	20	20
4	10	5	5
5	5	0.5	5
6	30	30	20
7	30	20	30
8	20	10	10
9	10	10	10
10	10	10	5
12	10	5	5
Chloramphenicol	0.1	0.1	0.1

groups, which makes slow diffusion through the cell membrane. In general, the antibacterial study shows some promising results compare to the standard drug, Table 1.

The minimum inhibitory concentration (MIC) values of the studied compounds against these bacteria are reported in Table 2. Compound **5** (MIC = 0.5 μg/ml) was found to have a very good activity against *E. coli* when compared with chloramphenicol and good activity against *S. aureus* and *P. aeruginosa*.

Compounds **1**, **2**, **4** and **12** were found to be equally potent to against *E. coli* and *P. aeruginosa*.

In general, compounds **1**–**10** and **12** showed some promising activity against the growth of the tested bacterial strains. In comparing the biological activity of these newly synthesized with those previously reported data on ferrocene derivatives [16–18], we may conclude that the combination of ferrocene and selenazoles/selenadiazoles is favorable for the biological activity.

Conclusion

In conclusion, the objective of the present work was to synthesize some novel ferrocene derivatives containing selenazole moieties and the new 3,5-diferrocenyl-1,2,4-selenadiazole in hope of discovering new compounds as antimicrobial agents. Some of these compounds showed potential biological activity against different strains of bacteria.

Experimental

Physical measurements

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Ultra-300 spectrometer in $CDCl_3$ solution with TMS as internal standard. Elemental analyses were determined on an MT-3 elemental analyzer within ±5% of the theoretical values. Mass spectra were recorded on an HP-598 8A MS instrument at 70 eV.

Synthesis

All materials were obtained from Sigma–Aldrich and solvents were purified and dried prior to use according to conventional methods. All reactions were carried out under nitrogen atmosphere and monitored by TLC using aluminum-backed plates coated with silica gel (Merck Kieselgel 60 F254). Acetyl ferrocene [19] and (2-bromoacetyl) ferrocene [20,21] were prepared by literature methods.

Phenylselenocarboxamide, 4-bromophenylseleno-carboxamide, 4-phenylphenylselenocarbox-amide, 4-methoxyphenyl selenocarboxamide, 4-methylthiophenylselenocarboxamide, 6-methoxynaphthyl-1-selenocarboxamide, 4-methoxynaphthyl-2-selenocarboxamide, 4-ethoxyphenylselenocarboxamide, 3,4-dimethoxyphenylselenocarboxamide and 3,5-dimethoxyphenyl-3,5-selenocarboxamide were prepared according to a literature method [10].

All compounds were characterized by their melting points, IR and ^{1}H NMR spectroscopic data.

1-Cyanoferrocene was prepared by a literature method [22,23] as golden-yellow plates in 28% yield, m.p.: 105–107 °C (Lit. [19] 106–107 °C; Lit. [23] 106.4–106.7 °C). IR (KBr disc): 3050, 2980, 2252, 1600, 1450, 870 cm^{-1}.

2-Ary-4-ferrocenyl-1,3-selenazoles were prepared from the reaction of the corresponding aryl selenocarboxames with (2-bromoacetyl)ferrocene by the following procedure:

A solution of (2-bromoacetyl)ferrocene (10 mmol) in of ethanol (10 mL) was added dropwise to a hot solution of aryl selenocarboxamides (10 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 60 min (the end of the reaction was monitored by TLC). The mixture is then concentrated by a rotary evaporator and the residue neutralized with dilute aqueous ammonia solution (10%). The precipitate was deposited, collected by filtration and then washed several times with cold ethanol. Recrystallization from ethanol gave the corresponding 2-ary-4-ferrocenyl-1,3-selenazoles in fair to good yields.

*2-Phenyl-4-ferrocenyl-1,3-selenazole (**1**)*

Yield: 66%, m.p. 119–121 °C.

Anal. Calc. for $C_{19}H_{15}FeNSe$: C, 58.20; H, 3.86; N, 3.57. Found: C, 58.12; H, 3.91; N, 3.35.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.75 (s, 1H, selenazole), 7.87 (m, 2H, Ar–*H*), 7.47 (m, 3H, Ar–*H*), 4.64 (t, 2H, $J = 1.82$ Hz, Cp), 4.36 (t, 2H, $J = 1.83$ Hz, Cp), 4.06 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 165.1, 160.3, 131.5, 123.6, 115.3, 78.2, 71.2, 68.6.

MS: *m*/*z*: 392 (M^+).

*2-(4-Bromophenyl)-4-ferrocenyl-1,3-selenazole (**2**)*

Yield: 55%, m.p. 146–148 °C.

Anal. Calc. for $C_{19}H_{14}BrFeNSe$: C, 48.45; H, 3.00; N, 2.97. Found: C, 48.26; H, 3.11; N, 3.05.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.82 (s, 1H, selenazole), 7.97 (d, 2H, $J = 7.8$ Hz, Ar–*H*), 7.65 (d, 2H, $J = 7.65$ Hz, Ar–*H*), 4.60 (t, 2H, $J = 1.82$ Hz, Cp), 4.30 (t, 2H, $J = 1.83$ Hz, Cp), 4.03 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 169.1, 163.6, 131.7, 131.4, 129.8, 125.5, 81.1, 70.2, 69.7, 58.1. MS: *m*/*z*: 470/472/544 (M^+).

*2-(4-Phenyphenyl)-4-ferrocenyl-1,3-selenazole (**3**)*

Yield: 61%, m.p. 181–182 °C.

Anal. Calc. for $C_{25}H_{19}FeNSe$: C, 64.13; H, 4.09; N, 2.99. Found: C, 64.23; H, 3.95; N, 2.87.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.79 (s, 1H, selenazole), 8.07 (d, 2H, J = 7.5 Hz, Ar–*H*), 7.84 (d, 2H, J = 7.85 Hz, Ar–*H*), 7.64 (m, 2H, Ar–*H*), 7.37–7.47 (m, 3H, Ar–*H*), 4.65 (t, 2H, J = 1.84 Hz, Cp), 4.32 (t, 2H, J = 1.82 Hz, Cp), 4.11 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 165.3, 159.7, 144.2, 140.8, 131.3, 129.1, 128.0, 127.9, 127.6, 129.4, 81.5, 70.5, 69.6, 67.9.

MS: m/z: 468 (M^+).

*2-(4-(Methoxy)phenyl)-4-ferrocenyl-1,3-selenazole (**4**)*

Yield: 72%, m.p. 215–217 °C.

Anal. Calc. for $C_{20}H_{17}FeNOSe$: C, 56.90; H, 4.06; N, 3.32. Found: C, 57.22; H, 3.96; N, 3.35.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.80 (s, 1H, selenazole), 7.77 (d, 2H, J = 7.6 Hz, Ar–*H*), 7.01 (d, 2H, J = 7.74 Hz, Ar–*H*), 4.65 (t, 2H, J = 1.82 Hz, Cp), 4.32 (t, 2H, J = 1.83 Hz, Cp), 4.27 (s, 3H, OCH_3), 4.02 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 168.3, 163.9, 162.8, 130.2, 123.8, 118.4, 114.7, 81.7, 73.3, 69.7, 67.8, 55.2.

*2-(4-(Methylthio)phenyl)-4-ferrocenyl-1,3-selenazole (**5**)*

Yield: 58%, m.p. 175–177 °C.

Anal. Calc. for $C_{20}H_{17}FeNSSe$: C, 54.82; H, 3.91; N, 3.20. Found: C, 54.75; H, 3.86; N, 3.35.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.79 (s, 1H, selenazole), 7.77 (d, 2H, J = 7, 6 Hz, Ar–*H*), 7.42 (d, 2H, J = 7.85 Hz, Ar–*H*), 4.73 (t, 2H, J = 1.81 Hz, Cp), 4.36 (t, 2H, J = 1.85 Hz, Cp), 4.11 (s, 5H, Cp), 2.57 (s, 3H, SCH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 168.6, 163.8, 141.5, 128.8, 129.0, 126.1, 121.2, 75.1, 69.9, 68.8, 68.6, 17.2.

MS: m/z: 438 (M^+).

*2-(6-Methoxy-2-naphthyl)-4-ferrocenyl-1,3-selenazole (**6**)*

Yield: 43%, m.p. 107–109 °C.

Anal. Calc. for $C_{24}H_{19}FeNOSe$: C, 61.04; H, 4.06; N, 2.97. Found: C, 60.78; H, 3.94; N, 3.12.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.75 (s, 1H, selenazole), 8.26 (s, 1H, Ar–*H*), 7.81–7.97 (m, 2H, Ar–*H*), 7.56 (d, 1H, J = 7.5 Hz, Ar–H), 7.2 (d, 1H, J = 1.5 Hz, Ar–H). 6.84 (dd, 1H, J = 1.6 Hz, J = 7.76 Hz, Ar–H), 4.71 (t, 2H, J = 1.81 Hz, Cp), 4.37 (t, 2H, J = 1.85 Hz, Cp), 4.27 (s, 3H, OCH_3), 4.12 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 165.6, 160.1, 157.2, 141.8, 129.9, 129.6, 129.3, 127.4, 127.0, 126.2, 119.6, 118.8, 106.9, 78.9, 72.1, 69.2, 67.7, 56.7.

*2-(4-Methoxy-1-naphthyl)-4-ferrocenyl-1,3-selenazole (**7**)*

Yield: 37%, m.p. 91–93 °C.

Anal. Calc. for $C_{24}H_{19}FeNOSe$: C, 61.04; H, 4.06; N, 2.97. Found: C, 60.99; H, 3.97; N, 2.87.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.81 (s, 1H, selenazole), 7.81 (d, 2H, J = 7.6 Hz, Ar–*H*), 7.58–7.73 (m, 2H, Ar–*H*), 7.24–7.38 (m, 2H, Ar–H), 7.04 (d, 1H, J = 7.8 Hz, Ar–H), 4.71 (t, 2H, J = 1.81 Hz, Cp), 4.41 (t, 2H, J = 1.85 Hz, Cp), 4.27 (s, 3H, OCH_3), 4.00 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 167.4, 160.4, 157.1, 135.2, 127.6, 126.7, 125.4, 125.0, 123.5, 122.6, 119.4, 118.9, 104.6, 81.4, 78.4, 69.5, 68.2, 56.2.

*2-(4-Ethoxyphenyl)-4-ferrocenyl-1,3-selenazole (**8**)*

Yield: 62%, m.p. 126–128 °C.

Anal. Calc. for $C_{21}H_{19}FeNOSe$: C, 57.82; H, 4.39; N, 2.21. Found: C, 57.88; H, 3.97; N, 2.14.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.82 (s, 1H, selenazole), 7.77 (d, 2H, J = 7.82 Hz, Ar–H), 7.24 (d, 2H, J = 1.7 Hz, Ar–H), 4.83 (q, 2H, CH_2), 4.72 (m, 2H, Cp), 4.38 (m, 2H, Cp), 4.10 (s, 5H, Cp), 1.89 (t, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 167.6, 161.5, 159.7, 129.6, 121.5, 119.1, 115.2, 78.4, 69.6, 58.7, 66.9, 65.4, 15.1.

MS: m/z: 436 (M^+).

*2-(3,4-Dimethoxyphenyl)-4-ferrocenyl-1,3-selenazole (**9**)*

Yield: 51%, m.p. 141–143 °C.

Anal. Calc. for $C_{21}H_{19}FeNO_2Se$: C, 55.78; H, 4.24; N, 3.10. Found: C, 55.58; H, 3.98; N, 3.12.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.65 (s, 1H, selenazole), 7.31 (s, 1H, Ar–H), 7.34 (d, 1H, J = 1.86 Hz, Ar–H), 6.91 (d, 1H, J = 8.21 Hz, Ar–H), 4.73 (t, 2H, J = 1.84 Hz, Cp), 4.54 (t, 2H, J = 1.83 Hz, Cp), 4.27 (s, 3H, OCH_3), 4.26 (s, 3H, OCH_3), 4.21 (s, 5H, Cp).

*2-(3,5-Dimethoxyphenyl)-4-ferrocenyl-1,3-selenazole (**10**)*

Yield: 57%, m.p. 158–160 °C.

Anal. Calc. for $C_{21}H_{19}FeNO_2Se$: C, 55.78; H, 4.24; N, 3.10. Found: C, 55.57; H, 4.15; N, 3.04.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.89 (s, 1H, selenazole), 6.98 (s, 2H, Ar–H), 6.55 (s, 1H, Ar–H), 4.66 (t, 2H, J = 1.83 Hz, Cp), 4.33 (t, 2H, J = 1.78 Hz, Cp), 4.31 (s, 3H, OCH_3), 4.27 (s, 3H, OCH_3), 4.22 (s, 5H, Cp).

MS: m/z: 452 (M^+).

*Ferrocenyl selenocarboxamide (**11**)*

Sodium borohydride (1.02 g, 27 mmol)was added dropwise over 30 min to a suspension of selenium powder (1.98 g, 25 mmol) in dry ethanol (30 mL) under nitrogen atmosphere while hydrogen evolved vigorously. The resulting solution stirred for additional 30 min. Pyridine (4.1 mL, 50 mmol) and 1-cyanoferrocene (2.74 g; 13 mmol) were added to the resulting solution at room temperature. The solution was heated under reflux while hydrochloric acid (20 mL, 2 M) was added dropwise over 2 h. The solution was refluxed for 30 min then filtered hot. The filtrate was cooled to room temperature. Crushed ice was added in small portions with continuous stirring until the precipitation of ferrocenyl selenocarboxamide was completed. The red precipitate was recrystallized from benzene to give an orange solid in 27% yield, m.p. 121–123 °C.

Anal Calc. for $C_{11}H_{11}NFeSe$: C, 45.24, H, 3.89, N, 4.80. Found: C, 45.12, H, 4.05, N, 4.68.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 4.62 (t, J = 1.82 Hz, 2H, Cp), 4.42 (t, J = 1.84 Hz, 2H, Cp), 4.18 (s, 5H, Cp), 9.45 (sb, 1H, NH), 10.34 (sb, 1H, NH).

*3,5-Diferrocenyl-1,2,4-selenadiazole (**12**)*

To a solution of ferrocenyl selenocarboxamide (1.17 g; 4 mmol) in acetone (20 mL) an aqueous solution of Na_2PdCl_4 (0.2 mg; 1×10^{-4} mmol) was added. The solution was stirred at room temperature for 6 h. The resulting solution was filtered and the filtrate evaporated at room temperature to give 3,5-diferrocenyl-1,2,4-selenadiazole as a yellow–orange solid in 35% yield, m.p. 111–113 °C.

Anal. Calc. for $C_{22}H_{18}Fe_2N_2Se$: C, 52.74; H, 3.62; N, 5.59; Found: C, 52.83; H, 3.59; N, 5.36.

^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 4.73 (t, J = 1.82 Hz, 2H, Cp), 4.62 (t, J = 1.8 Hz, 2H, Cp), 4.42 (t, J = 1.84 Hz, 2H, Cp), 4.33 (t, J = 1.82 Hz, 2H, Cp), 4.11 (s, 5H, Cp), 4.08 (s, 5H, Cp).

^{13}C NMR (75 MHz, $CDCl_3$, δ/ppm): 173.6 (C-Fc), 166.2 (C-Fc), 84.25 (Cp), 72.72 (Cp), 71.31 (Cp), 69.42 (Cp).

Antibacterial activity

Compounds **1**–**10** and **12** were screened for their antibacterial activity in vitro following the protocol described previously [24]. The antibacterial effect was assayed against Gram positive bacteria viz., *S. aureus* and Gram negative *E. coli* and *P. aeruginosa* by the agar well diffusion method. The compounds were dissolved in DMF at different concentrations of 0.1, 0.5, 5, 10, 20, 30, 40, 50, 80 and 100 μg/ml. Mueller Hinton-agar plates were prepared and inoculum size for test strain was adjusted to 10^8 CFU/ml (colony forming unit per milliliter) by comparing the turbidity. Wells (9 mm) were made in the agar petri dishes. DMF was used as the negative control. The plates were incubated at 37 °C for 24 h. Zone of inhibition of bacterial growth around each well was measured in mm. The results were compared with the activity of chloramphenicol identical concentrations. The experiment was performed three times to minimize the errors. The minimum inhibitory concentration (MIC), defined as the lowest concentration of the test compound, which inhibits the visible growth, was determined visually after incubation for 24 h at 37 °C.

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