Synthesis and Antimicrobial Studies of Selenadiazolo Benzimidazoles

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An efficient and eco-friendly method has been developed for the synthesis of selenadiazolo benzimidazoles by the condensation of *N*-benzylbenzo[c][1,2,5]selenadiazole-4,5-diamine with various aromatic aldehydes catalyzed by xanthan sulfuric acid. All the synthesized compounds **5a–j** were evaluated for *in vitro* antibacterial activity against Gram-positive bacterial strains (*Bacillus subtilis, Staphylococcus aureus,* and *Streptococcus pyogenes*), and Gram-negative bacterial strains (*Escherichia coli, Klebsiella pneumonia,* and *Salmonella typhimurium*) and antifungal against *Aspergillus niger, Candida albicans,* and *Aspergillus flavus* (Fungi). Compound **5i** emerged as the most interesting compound in this series exhibiting excellent antimicrobial activity.

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INTRODUCTION

Benzimidazole and their derivatives are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds. For example, they represent potential antitumor agents [1], antimicrobial agents [2], HIV [3,4], herpes(HSV-1) [5], RNA [6], influenza [7] and also act as topoisomerase inhibitors [8], selective neuropeptide YY1 receptor antagonists [9], angiotensin II inhibitors [10], and smooth muscle cell-proliferation inhibitors [11]. Sulfur and selenium have many properties in common and much sulfur chemistry is mirrored by selenium chemistry. Selenium is the trace element controlled by gene in human body [12]. In recent past, selenium chemistry was explored steadily and selenium-based compounds exhibited appreciable pharmacological properties [13-17]. In continuation of our work on benzimidazole moiety [18,19], we herein report for the first time, in vitro antimicrobial activity of selenadiazolo benzimidazoles.

The traditional synthesis of benzimidazoles includes the condensation of *o*-phenylenediamine with carboxylic acid [20], or its derivatives like nitriles, imidates, or orthoesters [21] and the condensation of *o*-phenylenediamine with aldehyde in refluxing nitrobenzene [22] or in the presence of various acidic catalysts. However, most of the methods suffer from limitations such as moderate yields, long reaction times, harsh reaction conditions, or tedious workup procedures.

Recently, the direction of science and technology has been shifting more toward eco-friendly, natural product resources, and reusable catalysts. Thus, natural biopolymers are attractive candidates in the search for such solid support catalysts [23,24]. Among different biopolymers, xanthan is one of the most common biopolymers and has some unique properties which make it an attractive alternative to conventional organic or inorganic supports for catalytic applications. [25] Recently, sulfonated xanthan has been used as a biopolymeric solid support acid catalyst for the synthesis of α -amino nitriles [26]. This polymer has unlimited availability as a renewable agro-resource and is biodegradable. We herein disclose a simple and efficient procedure for the synthesis of selenadiazolo benzimidazoles catalyzed by XSA at room temperature in excellent yield.

RESULTS AND DISCUSSION

In our initial endeavor, we carried out the reaction of Nbenzylbenzo[c][1,2,5]selenadiazole-4,5-diamine (3.0 mmol) with various aldehydes (3.1 mmol) in presence of xanthan sulfuric acid (0.08 g) in chloroform (5 mL) under conventional and microwave irradiation conditions separately (Scheme 1), and the results are tabulated in Table 3. In method A [microwave (MW) irradiation], the reaction mixture was irradiated in a domestic microwave oven at 300 W over 30-s intervals in an open vessel for 15 min. The progress of the reaction was confirmed by thin-layer chromatography (TLC). At 300 W, only 50% of the reaction was completed, whereas at 450 W, the reaction successfully completed within 8 min. In method B [conventional], when the reaction was carried out at room temperature, the reaction successfully completed within 4 h. With these optimistic results in hand, further investigation was carried out for the catalytic



evaluation of XSA for the optimum reaction conditions. The increase in the amount of XSA up to 0.1 g did not show much difference in terms of yield or reaction time. However, in the absence of XSA, only 10% of the product was obtained even after stirring for 24 h. A range of aromatic and heteroaromatic aldehydes were subjected to reaction with *N*-benzylbenzo[c][1,2,5]selenadiazole-4,5-diamine in the presence of 0.08 g of XSA and chloroform as solvent. It was found that both aromatic and heteroaromatic aldehydes reacted equally good to afford the selenadiazolo benzimidazoles in excellent yields.

We first tested the suitability of various solvents for the transformation of the *N*-benzylbenzo[c][1,2,5]selenadiazole-4,5-diamine with various aldehydes to selenadiazolo benzimidazoles. Chloroform provided excellent yields (92%) and proved to be the solvent of choice, whereas ethanol (87%), methanol (79%), acetonitrile (73%), and water (59%) afforded lower yields.

This method offers several advantages like milder reaction conditions, shorter reaction times, cleaner reaction profiles, high yields, and simple experimental and isolation procedures making it an useful route to the synthesis of selenadiazolo benzimidazoles. The structures of the compounds **5a–j** were confirmed by IR, ¹H-NMR, ¹³C-NMR, mass spectrometry, and elemental analysis.

At first, we synthesized the starting material (4) for the formation of 5a-j. The first step involves the Hinsberg reaction [27] for the synthesis of the corresponding 4-chloro selenadiazole in dry chloroform followed by nitration, amination, and then treating the product with sodium dithionate in boiled water to afford *N*-benzylbenzo[c][1,2,5] selenadiazole-4,5-diamine (4) in quantitative yield (Scheme 1).

BIOLOGICAL ACTIVITIES

Antibacterial and antifungal activities. All the newly synthesized benzimidazole derivatives (5a-j) were tested for their *in vitro* antibacterial activity against Gram-

bacterial strains (Bacillus subtilis positive [BS], Staphylococcus aureus [SA], and Streptococcus pyrogenes [SP]), and Gram-negative bacterial strains (Escherichia coli [EI], Klebsiella pneumonia [KP], and Salmonella typhimurium [ST]) using the agar-diffusion assay [28,29]. The antibiotic drug, ampicillin, was also used as a positive control. Antibacterial screening for analogs and positive control was performed at a fixed concentration of 1000 µg/mL. All 10 compounds represented in Table 1 exhibited antibacterial activity against both Gram-positive and Gram-negative bacterial strains with zones of inhibition (ZOI) ranging from 15 to 50 mm (Table 1). Analogs (5a-j) were also examined for their antifungal activity against different fungal strains, i. e., Aspergillus niger [AN], Candida albicans [CA], and Aspergillus flavus [AF] (Table 1). The anti-fungal drug, ketoconazole, was used as a positive control. The fungal strains were grown and maintained on Sabouraud glucose agar plates. The plates were incubated at 26°C for 72 h and resulting ZOIs were measured [30]. Antifungal screening for analogs and positive control was performed at a fixed concentration of 1000 µg/mL.

The minimum inhibitory concentration (MIC) of analogs (5a-j) and the positive control drugs ampicillin and ketoconazole was determined against the six bacterial strains and the three fungal strains by the liquid dilution method [31,32]. Concentrations of analogs and positive control drugs at 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 µg/mL were prepared in an appropriate solvent. Inoculums of the bacterial and fungal cultures were also prepared. Inoculum (0.2 mL) and sterile water (3.8 mL) were added to a series of tubes each containing 1 mL of test compound solution at the 10 different concentrations. The tubes were incubated for 24 h and carefully observed for the presence of turbidity. The minimum inhibitory concentration at which no growth was observed was taken as the MIC value. The MIC values for all the analogs examined ranged from 2.5 to 50 µg/mL. Several analogs exhibited superior

	Zone of	inhibition of se	elenadiazolo be	enzimidazoles (5a–j) analogs	against differei	nt bacteria and	fungi.		
	Zone of inhibition (mm)									
	Bacteria ^a			Bacteria ^b			Fungi ^c			
Analog	BS	SA	SP	EC	KP	ST	AN	CA	AF	
5a	21	24	26	29	34	27	25	29	30	
5b	29	39	28	15	30	20	35	29	32	
5c	35	40	38	36	36	35	25	23	29	
5d	29	35	30	35	40	42	35	35	38	
5e	30	25	30	25	25	26	27	32	35	
5f	25	24	23	38	30	25	20	15	25	
5g	30	20	25	25	25	19	20	25	35	
5h	25	25	30	38	25	25	30	30	34	
5i	40	50	39	44	47	46	38	35	38	
5j	25	32	26	20	30	35	24	35	25	
AMP^d	35	44	33	37	40	42	_	_	_	
KET ^e	_	_	_	_	_	_	41	38	33	

 Table 1

 Zone of inhibition of selenadiazolo benzimidazoles (5a-i) analogs against different bacteria and fung

^aGram-positive bacteria: BS, Bacillus subtilis; SA, Staphylococcus aureus; SP, Streptococcus pyogenes.

^bGram-negative bacteria: EC, Escherichia coli; KP, Klebsiella pneumonia; ST, Salmonella typhimurium.

^cAN, Aspergillus niger; CA, Candida albicans; AF, Aspergillus flavus.

^dAMP, ampicillin.

^eKET, ketoconazole

antimicrobial activity compared with the positive control drugs, ampicillin and ketoconazole. The MIC data for all the analogs against the different bacterial and fungal strains is shown in Table 2.

Antimicrobial activity. The data of the antimicrobial activity of the compounds and the control drugs as MIC (g/mL) values are given in Table 2. To observe the efficiency of the antimicrobial activity, ampicillin and

ketoconazol were used as reference antimicrobial agents. Antibacterial screening for analogs and positive control was performed at a fixed concentration of 1000 μ g/mL. All 10 compounds exhibited antibacterial activity against both Gram-positive and Gram-negative bacterial strains with ZOI ranging from 15 to 50 mm (Table 1). Analog **5i** (ZOI_[BS] = 40 mm, ZOI_[SA] = 50 mm, ZOI_[SP] = 39 mm, ZOI_[EC] = 44 mm, ZOI_[KP] = 47 mm, and ZOI_[ST] = 46 mm)

 Table 2

 Minimum inhibitory concentration values for selenadiazolo benzimidazoles (5a-j) analogs and positive control drugs against different bacteria and fungi.

	Minimum inhibitory concentration (µg/mL)									
	Bacteria ^a			Bacteria ^b			Fungi ^c			
Analog	BS	SA	SP	EC	KP	ST	AN	CA	AF	
5a	40	30	25	35	30	25	25	30	25	
5b	35	40	30	45	25	25	30	40	25	
5c	25	35	50	20	25	35	30	45	25	
5d	45	40	25	15	30	35	25	20	10	
5e	40	10	45	40	25	10	45	40	20	
5f	20	15	45	20	25	20	35	30	25	
5g	40	25	45	45	25	35	40	45	35	
5h	30	30	40	25	25	35	30	25	10	
5i	2.5	2.5	5	2.5	15	10	15	15	10	
5j	35	15	25	20	30	10	15	15	10	
AMP^d	20	10	25	15	10	10	_	_	_	
KET ^e	_	_	-	_	_	-	15	25	15	

^aGram-positive bacteria: BS, *Bacillus subtilis*; SA, *Staphylococcus aureus*; SP, *Streptococcus pyogenes*.

^bGram-negative bacteria: EC, Escherichia coli; KP, Klebsiella pneumonia; ST, Salmonella typhimurium.

^cAN, Aspergillus niger; CA, Candida albicans; AF, Aspergillus flavus.

^dAMP, ampicillin.

^eKET, ketoconazole.

was identified as a potent antibacterial agent against all Gram-positive and Gram-negative bacterial strains (Table 1).

Analogs (**5a–j**) were also examined for their antifungal activity against different fungal strains, i.e., *Aspergillus niger* [AN], *Candida albicans* [CA], and *Aspergillus flavus* [AF]. The anti-fungal drug, ketoconazole, was used as a positive control. Antifungal screening for analogs and positive control was performed at a fixed concentration of 1000 µg/mL. Analog **5i** (ZOI_[AN] = 38 mm, ZOI_[CA] = 35 mm, and ZOI [AF] = 38 mm), **5d** (ZOI_[CA] = 35 mm ZOI_[AF] = 38 mm), and **5j** (ZOI_[CA] = 35 mm) were identified as the most potent antifungal agent against all three fungal strains (Table 1).

The MIC values for all the analogs examined ranged from 2.5 to 50 µg/mL. Several analogs exhibited superior antimicrobial activity compared with the positive control drugs, ampicillin and ketoconazole. Analogs 5i (MIC_[BS] = 2.5 μ g/mL, MIC_[SA] = 2.5 μ g/mL, MIC_[SP] = 5 μ g/mL, $MIC_{[EC]} = 2.5 \ \mu g/mL$, $MIC_{[KP]} = 15 \ \mu g/mL$, $MIC_{[ST]} =$ 10 μ g/mL), **5e** (MIC_[ST] = 10 μ g/mL), and **5j** (MIC_[ST] = 10 µg/mL) were identified as potent anti-bacterial agent, and analogs 5i (MIC_[AN] = 15 μ g/mL, MIC_[CA] = 15 μ g/ mL, MIC_[AF] = 10 μ g/mL), **5j** (MIC_[AN] = 15 μ g/mL, $MIC_{[CA]} = 15 \ \mu g/mL, MIC_{[AF]} = 10 \ \mu g/mL), 5h \ (MIC_{[AF]})$ = 10 μ g/mL), and **5d** (MIC_[AF] = 10 μ g/mL) were identified as potent anti-fungal agents. Based on the MIC data, analogs 5i was identified as the most potent antimicrobial agent. The MIC data for all the analogs against the different bacterial and fungal strains is shown in Table 2.

CONCLUSIONS

In summary, we have developed a convenient method to synthesize selenadiazolo benzimidazoles with high yields from N-benzylbenzo[c][1,2,5]selenadiazole-4,5-diamine, aldehydes, and XSA in chloroform, and evaluated for their antimicrobial activity against different bacterial and fungal strains. Analog **5i** was considered lead compound worthy of further structural optimization and development as

potential antimicrobial agent for the treatment of bacterial and fungal infections.

EXPERIMENTAL

All the melting points were uncorrected. The progress of the reaction was monitored by (TLC). IR spectra (KBr) were recorded on Shimadzu FTIR model 8010 spectrometer and the ¹H-NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as internal standard. The C, H, and N analysis of the compound was done on a Carlo Erba model EA1108. Mass spectra were recorded on a JEOL JMS D-300 Spectrometer. All solvents and reagents were purchased from Aldrich and Fluka firms.

General procedure for the synthesis of selenadiazolo benzimidazoles. *Method A (microwave irradiation)*. A mixture of *N*-benzylbenzo[c][1,2,5]selenadiazole-4,5-diamine (3.0 mmol), aldehyde (3.1 mmol), and xanthan sulfuric acid in chloroform (5 mL) was taken in an open vessel, placed in microwave oven and irradiated at 450 W power for appropriate time (Table 3). After completion of the reaction (confirmed by TLC), the solvent was evaporated under vacuum on a rotary evaporator. The crude product was purified by column chromatography on silica gel using ethyl acetate-hexane (2:8) as eluent to afford corresponding pure products in good yields.

Method B (conventional method). Mixture of *N*-benzylbenzo [c][1,2,5]selenadiazole-4,5-diamine (3.0 mmol), aldehyde (3.1 mmol), and xanthan sulfuric acid in chloroform (5 mL) was stirred at room temperature for appropriate time (Table 3). After completion of the reaction (confirmed by TLC), the solvent was evaporated under vacuum on a rotary evaporator. The crude product was purified by column chromatography on silica gel using ethyl acetate-hexane (2:8) as eluent to afford corresponding pure products in good yields.

Analog 5a. Mp: 230°C IR (KBr, cm⁻¹): 3064, 1621; ¹H-NMR (DMSO): $\delta = 4.03$ (s, 2H), 7.08–7.34 (m, 10H), 7.37 (d, 1H), 7.69 (d, 1H); ¹³C-NMR (DMSO): $\delta = 43.2$, 121.5, 121.7, 123.9, 127.2, 128.7, 128.8, 129.3, 129.4, 130.8, 133.9, 134.6, 135.7, 138.1, 138.5, 151.7, 160.1, 162.0; EIMS, 70 eV, *m/z*: 390 (M⁺); Anal. Calcd. for C₂₀H₁₄N₄Se: C, 61.70; H, 3.62; N, 14.39. Found: C, 60.54; H, 4.29; N, 13.77.

Synthesis of selenadiazolo benzimidazoles.							
Analog		Meth	od A	Method B			
	Aldehyde	Time (min)	Yield ^a (%)	Time (h)	Yield ^a (%)		
5a	Benzaldehyde	8	92	4	85		
5b	4-Chlorobenzaldehyde	8	89	4	81		
5c	4-Nitrobenzaldehyde	8	88	4	83		
5d	4-Methylbenzaldehyde	8	90	4	83		
5e	4-Methoxybenzaldehyde	8	91	4	85		
5f	4-Hydroxybenzaldehyde	8	89	4	81		
5g	2-Hydroxybenzaldehyde	8	87	4	80		
5h	2-Naphthaldehyde	8	83	4	77		
5i	2-Furaldehyde	8	82	4	75		
5j	4-Ethoxybenzaldehyde	8	88	4	79		

 Table 3

 Synthesis of selenadiazolo benzimidazoles.

^aYields refer to isolated products and all synthesized compounds were characterized by spectral data (IR, ¹H-NMR, ¹³C-NMR, mass, and C, H, and N analysis).

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Analog **5b**. Mp: 273°C IR (KBr, cm⁻¹): 3060, 1630; ¹H-NMR (DMSO): $\delta = 4.09$ (s, 2H), 7.06–7.40 (m, 9H), 7.47 (d, 1H), 7.79(d, 1H); ¹³C-NMR (DMSO): $\delta = 43.1$, 121.6, 121.4, 123.8, 127.3, 128.9, 129.0, 129.1, 129.5, 130.9, 133.5, 134.4, 135.8, 138.2, 143.5, 151.6, 160.2, 162.5; EIMS, 70 eV, *m/z*: 424 (M⁺); Anal. Calcd. for C₂₀H₁₃ClN₄Se: C, 56.69; H, 3.09; N, 13.22. Found: C, 58.23; H, 3.68; N, 12.64.

Analog 5c. Mp: 196°C IR (KBr, cm⁻¹): 3049, 1640; ¹H-NMR (DMSO): δ = 4.11 (s, 2H), 7.15–7.45 (m, 9H), 7.49 (d, 1H), 7.85 (d, 1H), ¹³C-NMR (DMSO): δ = 42.9, 120.8, 121.1, 123.7, 125.1, 125.6, 128.2, 129.4, 129.7, 130.4, 133.5, 134.1, 135.0, 138.3, 147.1, 153.0, 160.5, 162.2; EIMS, 70 eV, *m/z*: 435 (M⁺); Anal. Calcd. for C₂₀H₁₃N₅O₂Se: C, 55.31; H, 3.02; N, 16.13.Found: C, 56.11; H, 3.56; N, 17.22.

Analog 5d. Mp: 250°C IR (KBr, cm⁻¹): 3051, 1619; ¹H-NMR (DMSO): δ = 2.54 (s, 3H), 4.07 (s, 2H), 7.01–7.32 (m, 9H), 7.41 (d, 1H), 7.76 (d, 1H); ¹³C-NMR (DMSO): δ = 23.3, 43.5, 121.7, 121.1, 123.8, 127.8, 128.5, 128.5, 129.0, 129.6, 131.0, 134.0, 134.7, 135.6, 138.3, 138.4, 151.9, 160.3, 162.5; EIMS, 70 eV, *m/z*: 404 (M⁺); Anal. Calcd. for C₂₁H₁₆N₄Se: C, 62.53; H, 4.00; N, 13.89. Found: C, 62.12; H, 3.65; N, 12.92.

 62:35, H, 4.00, N, 13.89. Found: C, 62.12, H, 5.03, N, 12.92.

 Analog 5e.
 Mp: 276°C IR (KBr, cm⁻¹): 3059, 1628; ¹H

 NMR (DMSO): δ =3.63 (s, 3H), 4.08 (s, 2H), 7.07–7.39 (m,

 9H), 7.45 (d, 1H), 7.79 (d, 1H); ¹³C-NMR (DMSO): δ = 43.4,

 58.2, 116.2, 121.6, 122.4, 124.2, 127.3, 128.9, 128.5, 129.1,

 130.9, 133.5, 134.3, 135.5, 138.5, 152.0, 155.7, 160.3, 162.5;

 EIMS, 70 eV, m/z: 420 (M⁺); Anal. Calcd. for C₂₁H₁₆N₄OSe:

 C, 60.15; H, 3.85; N, 13.36. Found: C, 61.22; H, 4.52; N, 13.96.

 Analog 5f.
 Mp: 140–141°C IR (KBr, cm⁻¹): 3060, 1635;

 ¹H-NMR (DMSO): δ = 3.99 (s, 2H), 5.21 (s, 1H), 6.99–7.37

 (m, 9H), 7.39 (d, 1H), 7.72 (d, 1H); ¹³C-NMR (DMSO): δ =

 43.4, 117.3, 121.2, 122.3, 124.5, 127.3, 128.9, 128.1, 129.0,

 130.3, 133.5, 134.7, 135.2, 138.3, 152.1, 153.5, 160.5, 162.1;

 EIMS, 70 eV, m/z: 406 (M⁺); Anal. Calcd. for C₂₀H₁₄N₄OSe:

C, 59.27; H, 3.48; N, 13.82. Found: C, 57.91; H, 3.90; N, 14.23. *Analog* 5g. Mp: 248°C IR (KBr, cm⁻¹): 3057, 1640; ¹H-NMR (DMSO): δ = 4.00 (s, 2H), 5.21 (s, 1H), 7.01–7.35 (m, 9H), 7.40 (d, 1H), 7.74 (d, 1H); ¹³C-NMR (DMSO): δ = 43.4, 117.0, 118.9, 121.1, 122.6, 124.3, 127.0, 128.7, 128.4, 129.3, 130.5, 133.6, 134.7, 135.2, 138.1, 152.0, 154.0, 160.4, 162.2; EIMS, 70 eV, *m*/*z*: 406 (M⁺); Anal. Calcd. for C₂₀H₁₄N₄OSe: C, 59.27; H, 3.48; N, 13.82. Found: C, 57.92; H, 3.88; N, 14.27.

Analog **5h**. Mp: 194–195°C IR (KBr, cm⁻¹): 3058, 1645; ¹H-NMR (DMSO): δ = 4.13 (s, 2H), 7.15–7.44 (m, 12H), 7.51 (d,1H), 7.82 (d, 1H); ¹³C-NMR (DMSO): δ = 43.2, 121.7, 121.9, 123.5, 127.2, 128.2, 128.3, 128.5, 128.9, 129.0, 129.2, 130.3, 133.5, 134.2, 135.8, 136.2, 136.5, 138.0, 138.2, 152.1, 160.3, 162.5; EIMS, 70 eV, *m*/*z*: 440 (M⁺); Anal. Calcd. for C₂₄H₁₆N₄Se: C, 65.61; H, 3.67; N, 12.75. Found: C, 64.23; H, 3.11; N, 13.25.

Analog 5i. Mp: 222°C IR (KBr, cm⁻¹): 3054, 1665; ¹H-NMR (DMSO): $\delta = 4.08$ (s, 2H), 6.65–7.11 (m, 3H), 7.20–7.41 (m, 5H), 7.49 (d, 1H), 7.77 (d, 1H); ¹³C-NMR (DMSO): $\delta = 40.8$, 110.8, 112.5, 120.9, 121.5, 123.9, 127.2, 128.7, 129.3, 130.4, 134.6, 138.1,148.7, 150.1, 152.3, 160.1, 162.0; EIMS, 70 eV, *m/z*: 380 (M⁺); Anal. Calcd. for C₁₈H₁₂N₄OSe: C, 57.00; H, 3.19; N, 14.77. Found: C, 57.89; H, 3.27; N, 12.23.

Analog 5j. Mp: 196–197°C IR (KBr, cm⁻¹): 3058, 1633; ¹H-NMR (DMSO): δ = 1.45 (t, 3H), 3.97 (q, 2H), 4.06 (s, 2H), 7.09–7.33 (m, 9H), 7.46 (d, 1H), 7.80 (d, 1H); ¹³C-NMR (DMSO): δ = 19.8, 43.8, 65.8, 116.9, 121.8, 122.7, 124.5, 127.3, 128.7, 128.0, 129.5, 130.7, 133.4, 134.5, 135.3, 138.4, 152.1, 155.5, 160.6, 162.2; EIMS, 70 eV, *m/z*: 434 (M⁺); Anal. Calcd. for $C_{22}H_{18}N_4OSe$: C, 60.97; H, 4.19; N, 12.93. Found: C, 61.82; H, 4.08; N, 2.72.

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