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Synthesis of 4-Hetaryl-Substituted 5-Amino- and 5-Sulfanyl-1,3-oxazole Derivatives

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Abstract—Previously unknown 5-amino- and 5-sulfanyl-1,3-oxazole derivatives containing a 1,3,4-oxadiazole, 1,3,4-thiadiazole, or 1,2,4-triazole fragment at C^4 were synthesized from accessible 1,3-oxazole-4-carboxylic acid hydrazides.

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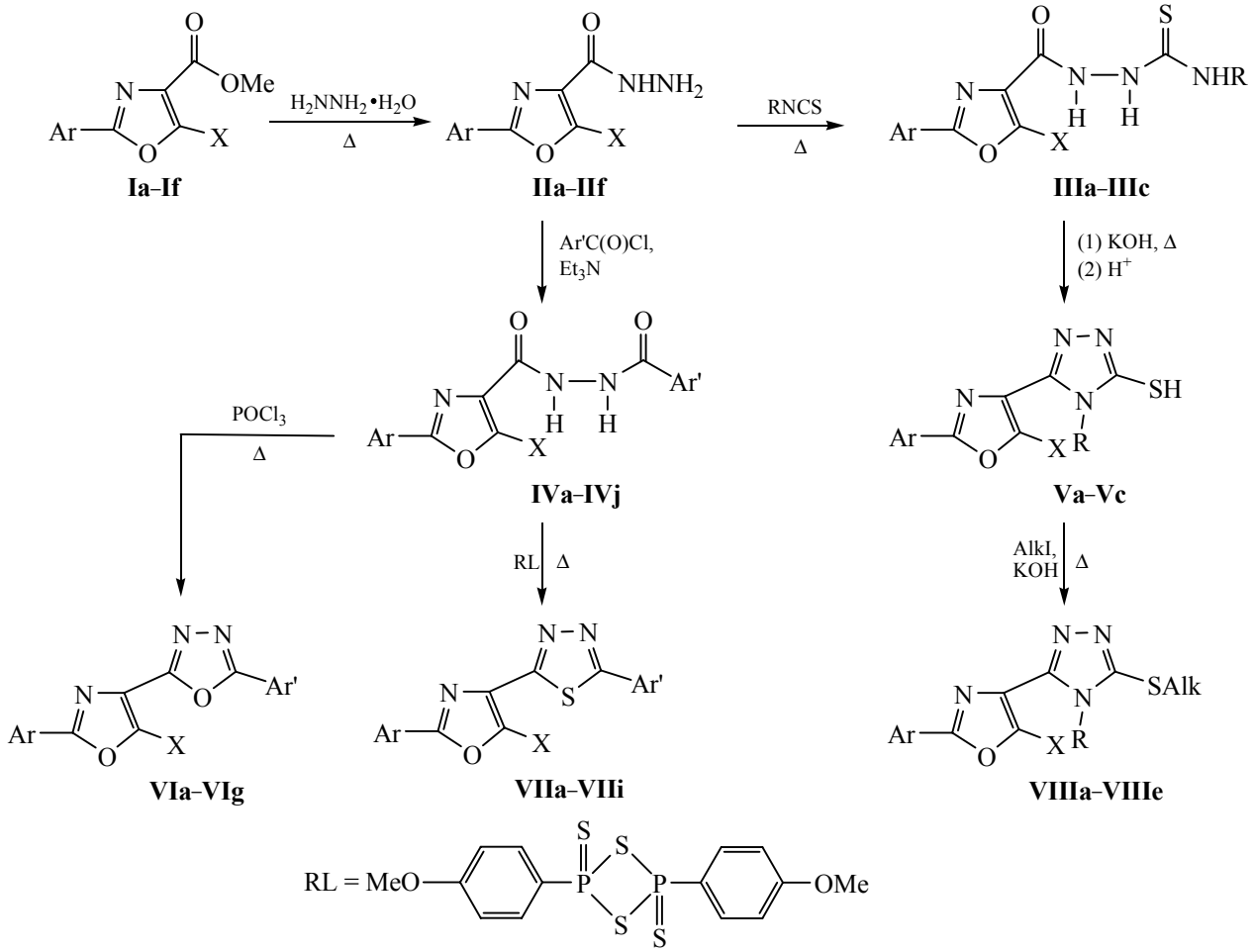
In the early 1950s J.W. Cornforth, who was one of the most prominent researchers of the chemistry of oxazoles, noted that oxazole derivatives rarely occurred in nature and that therefore they were not promising from the viewpoint of searching for new biologically active substances [1]. However, recent studies performed mostly during the past 30 years showed that various bacteria and marine organisms produced numerous antibiotics belonging to the oxazole series [2–5]. Moreover, numerous oxazole-based synthetic bioregulators are known, which exhibit strong antimicrobial, cytostatic, immune stimulating, neuroleptic, analgesic, and other kinds of biological activity [6–8]. In this connection, the synthesis of oxazole derivatives containing hetaryl substituents, in particular 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole fragments which could considerably affect bioregulator properties of oxazole, attracts certain interest, for the above heterocyclic fragments potentially possess a broad spectrum of biological properties [7, 10–15].

As key starting compounds for the synthesis of 4-hetaryl-substituted 5-amino- and 5-sulfanyl-1,3-oxazoles **V**–**VIII** we selected 1,3-oxazole-4-carboxylic acid hydrazides **II** that are readily obtainable from the corresponding esters **I** as shown in Scheme 1. Hydrazides **II** reacted with methyl and phenyl isothiocyanates to produce thiosemicarbazides **III** which readily underwent intramolecular cyclization in aqueous potassium hydroxide. The acidification with acetic acid precipitated triazoles **V** as colorless crystalline substances. The alkylation of compounds **V** with methyl or ethyl iodide in an alcoholic solution of potassium hydroxide afforded the corresponding *S*-alkyl derivatives **VIII** (Table 1).

Acylation of hydrazides **II** with benzoyl and *p*-methylbenzoyl chlorides occurred regioselectively at the primary amino group with the formation of *N*′-acyl-2-aryl-5-amino(or arylsulfanyl)-1,3-oxazole-4-carbohydrazides **IV**. The treatment of the latter with phosphoryl chloride or Lawesson's reagent resulted in cyclization to 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives **VI** and **VII** (Table 1). All 4-hetaryl-substituted 1,3-oxazoles **V**–**VIII** are characterized by the presence of an additional nitrogen- or sulfur-containing substituent in the 5-position of the oxazole ring, which is important from the viewpoint of biological activity [16–19].

The newly synthesized oxazole derivatives (Scheme 1) were chromatographically pure crystalline substances whose structure directly followed from the procedure of their preparation and was confirmed by the IR and ^{1}H NMR spectra (Table 2). The ^{1}H NMR spectra of **III** and **IV** lacked singlets at δ 4.32–4.34 and 8.82–8.92 ppm, which are typical of the NH_2 and NH protons, respectively, in initial hydrazides **II**; instead, two singlets appeared in the region δ 8.33–10.43 ppm; the latter disappeared as a result of formation of triazole, oxadiazole, or thiadiazole ring in the course of the transformations **III**→**V**, **IV**→**VI**, and **IV**→**VII**. Compounds **V** displayed in the ^{1}H NMR spectra a broadened signal in the region δ 10.90–



I, **II**, Ar = Ph (**a**, **c**, **e**, **f**), 4-MeC_6H_4 (**b**, **d**); X = piperidino (**a**, **b**), morpholino (**c**, **d**), 4-MeC_6H_4S (**e**), 4-ClC_6H_4S (**f**); **III**, **IV**, Ar = Ph (**a**–**d**, **g**–**j**), 4-MeC_6H_4 (**e**, **f**); Ar′ = Ph (**a**, **c**, **e**, **g**, **i**), 4-MeC_6H_4 (**b**, **d**, **f**, **h**, **j**); X = piperidino (**a**, **b**), morpholino (**c**–**f**), 4-MeC_6H_4S (**g**, **h**), 4-ClC_6H_4S (**i**, **j**); **V**, Ar = Ph (**a**), 4-MeC_6H_4 (**b**, **c**); R = Ph (**a**, **b**), Me (**c**); X = piperidino (**a**), morpholino (**b**, **c**); **VI**, Ar = Ph (**a**, **b**, **d**–**g**), 4-MeC_6H_4 (**c**); Ar′ = 4-MeC_6H_4 (**a**, **b**, **e**, **g**), Ph (**c**, **d**, **f**); X = piperidino (**a**), morpholino (**b**, **c**), 4-MeC_6H_4S (**d**, **e**), 4-ClC_6H_4S (**f**, **g**); **VII**, Ar = Ph (**a**–**c**, **f**–**i**), 4-MeC_6H_4 (**d**, **e**); Ar′ = 4-MeC_6H_4 (**a**, **c**, **e**, **g**, **i**), Ph (**b**, **d**, **f**, **h**); X = piperidino (**a**), morpholino (**b**–**e**), 4-MeC_6H_4S (**f**, **g**), 4-ClC_6H_4S (**h**, **i**); **VIII**, Ar = Ph (**a**, **b**), 4-MeC_6H_4 (**c**–**e**); R = Ph (**a**–**d**), Me (**e**); Alk = Me (**a**, **c**), Et (**b**, **d**, **e**); X = piperidino (**a**, **b**), morpholino (**c**–**e**).

11.36 ppm, which was assigned to the SH proton; no such proton was present in alkylation products **VIII**. No absorption was observed in the regions 1640–1700 and 3000–3600 cm^{-1} of the IR spectra of **VI** and **VII**, and their ^1H NMR spectra contained no signal at δ 9.60–10.43 ppm, which is typical of the NH proton in acylated hydrazides **IV**. The above findings suggest participation of the –C(O)NHNHC(O)– fragment in the intramolecular cyclization with the formation of oxadiazole or thiadiazole ring. In the ^1H NMR spectra of all compounds **V**–**VIII**, signals from aromatic and aliphatic protons with intensity ratios corresponding to the assumed structures were also observed.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Vertex 70 spectrometer. The ^1H NMR spectra were measured from solutions in DMSO-d_6 on a Varian VXR-300 spectrometer using tetramethylsilane as internal reference. The melting points were determined on a Fisher–Johns melting point apparatus.

Methyl 2-aryl-5-piperidino(or morpholino)-1,3-oxazole-4-carboxylates **Ia**–**Id** were synthesized as described in [20]. Methyl 2-aryl-5-arylsulfanyl-1,3-oxazole-4-carboxylates **Ie** and **If** were prepared according to the procedure described in [21].

Table 1. Yields, melting points, and elemental analyses of compounds **I**–**VIII**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			N	S (Cl)		N	S (Cl)
Ib	85	101–103 (hexane)	9.36	–	$C_{17}H_{20}N_2O_3$	9.33	–
Id	86	105–109 (EtOH)	9.33	–	$C_{16}H_{18}N_2O_4$	9.27	–
IIa	75	111–114 (cyclohexane)	19.41	–	$C_{15}H_{18}N_4O_2$	19.57	–
IIb	79	92–94 (cyclohexane)	18.59	–	$C_{16}H_{20}N_4O_2$	18.65	–
IIc	79	163–166 (EtOH)	19.33	–	$C_{14}H_{16}N_4O_3$	19.43	–
IId	80	135–138 (EtOH)	18.48	–	$C_{15}H_{18}N_4O_3$	18.53	–
IIf	85	153–156 (EtOH)	12.20	9.25 (10.33)	$C_{16}H_{12}ClN_3O_2S$	12.15	9.27 (10.25)
IIIa	75	151–153 (EtOH)	16.72	7.55	$C_{22}H_{23}N_5O_2S$	16.61	7.61
IVa	76	180–184 (EtOH)	14.25	–	$C_{22}H_{22}N_4O_3$	14.35	–
IVb	74	166–170 (EtOH)	13.95	–	$C_{23}H_{24}N_4O_3$	13.85	–
IVc	80	185–188 (MeCN)	14.35	–	$C_{21}H_{20}N_4O_4$	14.28	–
IVd	82	235–239 (MeCN–DMF, 3:1)	13.74	–	$C_{22}H_{22}N_4O_4$	13.78	–
IVe	84	194–196 (EtOH)	13.68	–	$C_{22}H_{22}N_4O_4$	13.78	–
IVf	82	202–205 (EtOH)	13.25	–	$C_{23}H_{24}N_4O_4$	13.32	–
IVg	89	192–196 (MeCN)	9.85	7.44	$C_{24}H_{19}N_3O_3S$	9.78	7.47
IVh	85	175–179 (MeCN)	9.35	7.19	$C_{25}H_{21}N_3O_3S$	9.47	7.23
IVi	90	186–189 (MeCN)	9.41	7.14 (7.95)	$C_{23}H_{16}ClN_3O_3S$	9.34	7.13 (7.88)
IVj	88	177–181 (MeCN)	9.09	6.93 (7.72)	$C_{24}H_{18}ClN_3O_3S$	9.06	6.91 (7.64)
Va	78	234–236 (EtOH)	17.39	7.91	$C_{22}H_{21}N_5OS$	17.36	7.95
Vb	82	258–262 (EtOH)	16.79	7.62	$C_{22}H_{21}N_5O_2S$	16.69	7.64
Vc	80	226–229 (EtOH)	19.62	8.95	$C_{17}H_{19}N_5O_2S$	19.59	8.97
VIa	71	173–175 (MeCN)	14.45	–	$C_{23}H_{22}N_4O_2$	14.50	–
VIb	70	199–203 (MeCN–DMF, 3:1)	14.28	–	$C_{22}H_{20}N_4O_3$	14.42	–
VIc	68	234–237 (EtOH–DMF, 1:1)	14.30	–	$C_{22}H_{20}N_4O_3$	14.42	–
VId	72	151–153 (MeCN)	10.26	7.75	$C_{24}H_{17}N_3O_2S$	10.21	7.79
VIe	69	152–154 (MeCN)	9.93	7.51	$C_{25}H_{19}N_3O_2S$	9.88	7.54
VIf	70	180–182 (MeCN)	9.61	7.45 (8.52)	$C_{23}H_{14}ClN_3O_2S$	9.73	7.42 (8.21)
VIg	72	191–193 (MeCN)	9.41	7.14 (8.05)	$C_{24}H_{16}ClN_3O_2S$	9.42	7.19 (7.95)
VIIa	86	200–203 (MeCN–DMF, 3:1)	13.81	7.90	$C_{23}H_{22}N_4OS$	13.92	7.97
VIIb	83	184–185 (MeCN–DMF, 3:1)	14.20	8.23	$C_{21}H_{18}N_4O_2S$	14.35	8.21
VIIc	81	197–200 (MeCN–DMF, 3:1)	13.65	8.07	$C_{22}H_{20}N_4O_2S$	13.85	7.93
VIId	79	214–216 (EtOH–DMF, 1:1)	13.75	8.08	$C_{22}H_{20}N_4O_2S$	13.85	7.93
VIIe	85	216–218 (MeCN–DMF, 3:1)	13.42	7.64	$C_{23}H_{22}N_4O_2S$	13.39	7.66
VIIf	90	158–162 (MeCN)	9.75	15.05	$C_{24}H_{17}N_3OS_2$	9.83	15.00
VIIg	89	182–184 (MeCN)	9.41	14.49	$C_{25}H_{19}N_3OS_2$	9.52	14.52
VIIh	83	189–192 (MeCN)	9.20	14.30 (8.12)	$C_{23}H_{14}ClN_3OS_2$	9.38	14.32 (7.91)
VIIi	85	208–210 (MeCN)	8.92	13.80 (7.75)	$C_{24}H_{16}ClN_3OS_2$	9.10	13.88 (7.67)
VIIIa	71	152–155 (cyclohexane)	16.85	7.55	$C_{23}H_{23}N_5OS$	16.77	7.68
VIIIb	79	170–173 (EtOH)	16.25	7.48	$C_{24}H_{25}N_5OS$	16.23	7.43
VIIIc	76	158–162 (cyclohexane)	16.03	7.42	$C_{23}H_{23}N_5O_2S$	16.15	7.40
VIIId	83	178–182 (EtOH)	15.55	7.06	$C_{24}H_{25}N_5O_2S$	15.65	7.16
VIIIe	74	150–182 (cyclohexane)	18.26	8.38	$C_{19}H_{23}N_5O_2S$	18.17	8.32

Table 2. IR and ^{1}H NMR spectra of compounds **I–VIII**

Comp. no.	IR spectrum (KBr),[a] ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
Ib	1693 (CO)	1.63 br.s and 3.73 br.s [10H, $(CH_2)_5N$], 2.35 s (3H, CH_3), 3.60 s (3H, OCH_3), 7.31–7.73 m (4H, C_6H_4)
Id	1703 (CO)	2.36 s (3H, CH_3), 3.67–3.74 m [11H, OCH_3, $O(CH_2)_4N$], 7.32–7.75 m (4H, C_6H_4)
IIa	1645 (CO), 3215–3420 (NH as., NH_2 as.)	1.61 br.s and 3.65 br.s [10H, $(CH_2)_5N$], 4.34 br.s (2H, NH_2), 7.47–7.86 m (5H, C_6H_5), 8.82 s (1H, NH)
IIc	1628 (CO), 3280–3400 (NH as., NH_2 as.)	3.72 m [8H, $O(CH_2)_4N$], 4.34 br.s (2H, NH_2), 7.48–7.88 m (5H, C_6H_5), 8.92 s (1H, NH)
IId	1653 (CO), 3270–3350 (NH as., NH_2 as.)	2.35 s (3H, CH_3), 3.71 m [8H, $O(CH_2)_4N$], 4.32 br.s (2H, NH_2), 7.32–7.77 m (4H, C_6H_4), 8.88 s (1H, NH)
IIf	1680 (CO), 3314–3415 (NH as., NH_2 as.)	4.33 br.s (2H, NH_2), 7.40–7.91 m (9H, C_6H_4, C_6H_5), 8.85 s (1H, NH)
IIIa	1672 (CO), 3130–3320 (NH as.)	1.72 br.s and 3.79 br.s [10H, $(CH_2)_5N$], 7.25–7.92 m (10H, C_6H_5), 8.33 br.s (2H, NH), 9.04 br.s (1H, NH)
IVb	1654 (CO), 1680 (CO), 3100–3340 (NH as.)	1.62 br.s and 3.70 br.s [10H, $(CH_2)_5N$], 2.38 s (3H, CH_3), 7.30–7.94 m (9H, C_6H_4, C_6H_5), 9.60 s (1H, NH), 10.24 s (1H, NH)
IVc	1649 (CO), 1685 (CO), 3150–3340 (NH as.)	3.74 br.s [8H, $O(CH_2)_4N$], 7.48–7.95 m (10H, C_6H_5), 9.73 s (1H, NH), 10.33 s (1H, NH)
IVd	1643 (CO), 1682 (CO), 3200–3360 (NH as.)	2.38 s (3H, CH_3), 3.73 br.s [8H, $O(CH_2)_4N$], 7.27–7.93 m (9H, C_6H_4, C_6H_5), 9.69 s (1H, NH), 10.25 s (1H, NH)
IVe	1673 (CO), 1695 (CO), 3100–3350 (NH as.)	2.36 s (3H, CH_3), 3.72 br.s [8H, $O(CH_2)_4N$], 7.29–7.90 m (9H, C_6H_4, C_6H_5), 9.63 s (1H, NH), 10.24 s (1H, NH)
IVf	1654 (CO), 1689 (CO), 3180–3320 (NH as.)	2.37 s (6H, CH_3), 3.72 br. s [8H, $O(CH_2)_4N$], 7.30–7.81 m (8H, C_6H_4), 9.61 s (1H, NH), 10.22 s (1H, NH)
IVg	1693 (CO),[b] 3100–3250 (NH as.)	2.34 s (3H, CH_3), 7.31–7.95 m (14H, C_6H_4, C_6H_5), 10.40 br. s (2H, NH)
IVh	1671 (CO),[b] 3150–3280 (NH as.)	2.33 s and 2.39 s (3H each, CH_3), 7.29–7.89 m (13H, C_6H_4, C_6H_5), 10.42 d (2H, NH)
IVi	1675 (CO),[b] 3100–3250 (NH as.)	7.30–7.88 m (14H, C_6H_4, C_6H_5), 10.41 br.s (2H, NH)
IVj	1673 (CO),[b] 3100–3280 (NH as.)	2.39 s (3H, CH_3), 7.32–7.93 m (13H, C_6H_4, C_6H_5), 10.43 br.s (2H, NH)
Va	–	1.66 br.s and 3.30 br.s [10H, $(CH_2)_5N$], 7.28–7.66 m (10H, C_6H_5), 11.36 s (1H, SH)
Vb	–	2.38 s (3H, CH_3), 3.35 br. s, 3.83 br. s [8H, $O(CH_2)_4N$], 7.17–7.55 m (9H, C_6H_4, C_6H_5), 11.07 br. s (1H, SH)
Vc	–	2.43 s (3H, CH_3), 3.46 m and 3.88 m [11H, CH_3, $O(CH_2)_4N$], 7.29–7.84 m (4H, C_6H_4), 10.90 s (1H, SH)
VIa	–	1.67 br.s and 3.67 br.s [10H, $(CH_2)_5N$], 2.41 s (3H, CH_3), 7.42–7.94 m (9H, C_6H_4, C_6H_5)
VIb	–	2.41 s (3H, CH_3), 3.71 br.s and 3.81 br.s [8H, $O(CH_2)_4N$], 7.40–7.94 m (9H, C_6H_4, C_6H_5)
VIc	–	2.38 s (3H, CH_3), 3.71 m and 3.81 m [8H, $O(CH_2)_4N$], 7.34–8.04 m (9H, C_6H_4, C_6H_5)
VId	–	2.32 s (3H, CH_3), 7.21–8.09 m (14H, C_6H_4, C_6H_5)
VIe	–	2.31 s (3H, CH_3), 2.43 s (3H, CH_3), 7.21–8.03 m (13H, C_6H_4, C_6H_5)
VIf	–	7.41–8.06 m (14H, C_6H_4, C_6H_5)
VIg	–	2.43 s (3H, CH_3), 7.40–8.04 m (13H, C_6H_4, C_6H_5)
VIIa	–	1.68 br.s and 3.74 br.s [10H, $(CH_2)_5N$], 2.38 s (3H, CH_3), 7.37–7.89 m (9H, C_6H_4, C_6H_5)
VIIb	–	3.81 br.s [8H, $O(CH_2)_4N$], 7.56–8.03 m (10H, C_6H_5)
VIIc	–	2.38 s (3H, CH_3), 3.80 m [8H, $O(CH_2)_4N$], 7.35–7.90 m (9H, C_6H_4, C_6H_5)

Table 2. (Contd.)

Comp. no.	IR spectrum (KBr),[a] ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm
VIId	–	2.38 s (3H, CH_3), 3.80 m [8H, $O(CH_2)_4N$], 7.33–7.98 m (9H, C_6H_4, C_6H_5)
VIIe	–	2.37 s (6H, CH_3), 3.78 m [8H, $O(CH_2)_4N$], 7.32–7.85 m (8H, C_6H_4)
VIIf	–	2.32 s (3H, CH_3), 7.19–8.02 m (14H, C_6H_4, C_6H_5)
VIIg	–	2.31 s (3H, CH_3), 2.41 s (3H, CH_3), 7.21–7.98 m (13H, C_6H_4, C_6H_5)
VIIh	–	7.40–8.03 m (14H, C_6H_4, C_6H_5)
VIIi	–	2.41 s (3H, CH_3), 7.38–8.05 m (13H, C_6H_4, C_6H_5)
VIIIa	–	1.69 br.s and 3.38 br.s [10H, $(CH_2)_5N$], 2.75 s (3H, SCH_3), 7.34–7.66 m (10H, C_6H_5)
VIIIb	–	1.45 m (3H, CH_3), 1.66 br.s and 3.37 br. s [10H, $(CH_2)_5N$], 3.31 m (2H, SCH_2), 7.34–7.66 m (10H, C_6H_5)
VIIIc	–	2.37 s (3H, CH_3), 2.74 s (3H, SCH_3), 3.49 m and 3.87 m [8H, $O(CH_2)_4N$], 7.15–7.52 m (9H, C_6H_4, C_6H_5)
VIIId	–	1.45 t (3H, CH_3), 2.37 s (3H, CH_3), 3.30 m (2H, SCH_2), 3.49 m and 3.86 m [8H, $O(CH_2)_4N$], 7.15–7.52 m (9H, C_6H_4, C_6H_5)
VIIIe	–	1.48 t (3H, CH_3), 2.42 s (3H, CH_3), 3.30 m (2H, SCH_2), 3.56 m and 3.86 m [11H, $O(CH_2)_4N$, CH_3], 7.29–7.84 m (4H, C_6H_4)

[a] The IR spectra of **V**–**VIII** lack absorption bands in the regions 1640–1700 and 3000–3600 cm^{-1}. [b] Weak band with a shoulder.

2-Aryl-5-piperidino(or morpholino)-1,3-oxazole-4-carbohydrazides IIa–IId *(general procedure).* Hydrazine hydrate, 0.015 mol, was added to a solution of 0.005 mol of compound **Ia**–**Id** in 20 ml of methanol. The mixture was heated for 3 h under reflux and was left to stand for 12 h at 20–25°C. The precipitate was filtered off, washed with water, dried, and purified by recrystallization.

2-Aryl-5-arylsulfanyl-1,3-oxazole-4-carbohydrazides IIe and IIf *(general procedure).* Hydrazine hydrate, 0.015 mol, was added to a solution of 0.005 mol of compound **Ie** or **If** in 20 ml of methanol. The mixture was heated for 3 h under reflux and was left to stand for 12 h at 20–25°C. The precipitate was filtered off, washed with water, dried, and purified by recrystallization.

1-{[2-Aryl-5-piperidino(or morpholino)-1,3-oxazol-4-yl]carbonyl}-4-methyl(or phenyl)thiosemicarbazides IIIa–IIIc *(general procedure).* A mixture of 0.005 mol of compound **IIa** or **IId** and 0.005 mol of methyl or phenyl isothiocyanate in 10 ml of anhydrous dioxane was heated for 3 h under reflux. The mixture was then left to stand for 12 h at 20–25°C, the solvent was removed under reduced pressure, and the residue was treated with water and used in further syntheses without additional purification. An analytical sample of compound **IIIa** was obtained by recrystallization from ethanol.

***N′*-Aroyl-2-aryl-5-piperidino(or morpholino)-1,3-oxazole-4-carbohydrazides IVa–IVf** *(general procedure).* Compound **IIa**–**IId**, 0.005 mol, was dissolved in 30 ml of anhydrous acetonitrile, 0.005 mol of triethylamine and 0.005 mol of benzoyl or 4-methylbenzoyl chloride were added, and the mixture was heated for 3 h under reflux and left to stand for 12 h at 20–25°C. The mixture was diluted with 80 ml of water, and the precipitate was filtered off, dried, and purified by recrystallization.

***N′*-Aroyl-2-aryl-5-arylsulfanyl-1,3-oxazole-4-carbohydrazides IVg–IVj** *(general procedure).* Compound **IIe** or **IIf**, 0.005 mol, was dissolved in 30 ml of anhydrous acetonitrile, 0.005 mol of triethylamine and 0.005 mol of benzoyl or 4-methylbenzoyl chloride were added, and the mixture was heated for 3 h under reflux and left to stand for 12 h at 20–25°C. The mixture was diluted with 80 ml of water, and the precipitate was filtered off, dried, and purified by recrystallization.

3-[2-Aryl-5-piperidino(or morpholino)-1,3-oxazol-4-yl]-4-methyl(or phenyl)-1,2,4-triazole-5-thiols Va–Vc *(general proocedure).* A mixture of 0.004 mol of compound **IIIa**–**IIIc** and 0.008 mol of potassium hydroxide in 20 ml of water was heated for 3 h at the boiling point. The mixture was left to stand for 12 h at 20–25°C and acidified with acetic acid to pH ~4–5, and the precipitate was filtered off, washed with water, dried, and purified by recrystallization.

5-Aryl-2-[2-aryl-5-piperidino(or morpholino)-1,3-oxazol-4-yl]-1,3,4-oxadiazoles VIa–VIc *(general procedure).* A solution of 0.002 mol of compound

IVb–IVe in 5 ml of $POCl_3$ was heated for 6 h under reflux. The mixture was cooled to 20–25°C and poured onto ice, and the precipitate was filtered off, dried, and purified by recrystallization.

5-Aryl-2-[2-aryl-5-arylsulfanyl-1,3-oxazol-4-yl]-1,3,4-oxadiazoles VId–VIg *(general procedure).* A solution of 0.002 mol of compound **IVg–IVj** in 5 ml of $POCl_3$ was heated for 6 h under reflux. The mixture was cooled to 20–25°C and poured onto ice, and the precipitate was filtered off, dried, and purified by recrystallization.

5-Aryl-2-[2-Aryl-5-piperidino(or morpholino)-1,3-oxazol-4-yl]-1,3,4-thiadiazoles VIIa–VIIe *(general procedure).* A mixture of 0.002 mol of compound **IVb–IVf** and 0.003 mol of Lawesson's reagent in 10 ml of anhydrous dioxane was heated for 8 h under reflux. The mixture was kept for 12 h at 20–25°C, the solvent was removed under reduced pressure, the residue was treated with a 5% aqueous solution of sodium hydroxide, and the precipitate was filtered off, washed with water, dried, and purified by recrystallization.

5-Aryl-2-[2-aryl-5-arylsulfanyl-1,3-oxazol-4-yl]-1,3,4-thiadiazoles VIIf–VIIi *(general procedure).* A mixture of 0.002 mol of compound **IVg–IVj** and 0.002 mol of Lawesson's reagent in 10 ml of anhydrous dioxane was heated for 8 h under reflux. The mixture was kept for 12 h at 20–25°C, the solvent was removed under reduced pressure, the residue was treated with a 5% aqueous solution of sodium hydroxide, and the residue was filtered off, washed with water, dried, and purified by recrystallization.

3-[2-Aryl-5-piperidino(or morpholino)-1,3-oxazol-4-yl]-4-methyl(or phenyl)-5-methyl(or ethyl)sulfanyl-1,2,4-triazoles VIIIa–VIIIe *(general procedure).* Methyl or ethyl iodide, 0.002 mol, was added to a solution of 0.002 mol of compound **Va–Vc** and 0.002 mol of potassium hydroxide in 10 ml of ethanol. The mixture was heated for 1 h under reflux and cooled, the solvent was removed under reduced pressure, the residue was treated with 80 ml of water, the mixture was kept for 12 h at 20–25°C, and the precipitate was filtered off, dried, and purified by recrystallization.

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