Convenient Syntheses of 5-[(2-Methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole-2(3*H*)thione and N-Substituted 2-amino-5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazoles

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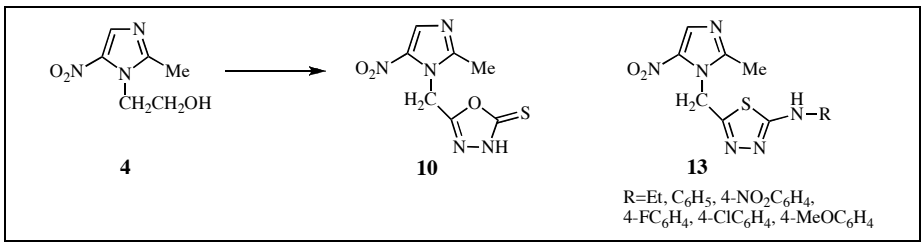

Oxidation of metronidazole (**4**) with sodium dichromate yielded the corresponding 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid (**5**) which was esterified with 1-butanol to give butyl 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetate (**8**). Reaction of the latter with hydrazine hydrate gave 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetohydrazide (**9**). Compound 5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**10**) could be obtained through the reaction of compound **9** with carbon disulfide in basic medium. Subsequent alkylation of compound **10** afforded alkyl 2-(5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazol-2-ylthio)acetate (**11**) in good yield. Reaction of hydrazide **9** with substituted isothiocynate yielded 1-[2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetyl]-4-aryl(or ethyl)thiosemicarbazide (**12**) which was cyclized in acidic media to N-substituted 2-amino-5-[(2-methyl-5-nitro-1H-imidazol-1-yl)methyl]-1,3,4-thiadiazole (**13**).

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INTRODUCTION

In general, 5-nitroimidazoles like metronidazole or ornidazole (Figure 1) are valuable drugs for treatment, of several protozoal diseases as well as for treating infections due to anaerobic bacteria [1]. The nitroimidazoles used therapeutically are 5-nitroimidazoles that have substituents at N-1 and C-2 but lack a substituent at C-4 [2], whereas the 4-nitroimidazoles have no significant therapeutic value [3-4]. Synthesis of biologically active 5-nitro isomer derivatives through N-alkylation of 4(5)-nitro-1*H*-imidazole seems to be complicated as a result of intrinsic low yield and poor regioselectivity of this type of reactions [5]. Besides, synthesis of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives have a great deal of importance because of their broad spectrums of biological characteristics such as anti-inflammatory, anti-fungal and anti-bacterial activities [6-13]. As an extension of our previous work on the synthesis of small bioactive heterocyclic molecules [14-17], we wish to report the synthesis of 5-[(2-methyl-5-nitro-1*H*-imidazole-1-yl)-methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**10**) and its methyl and ethyl thioacetate derivatives **11a-b**, and N-substituted 2-amino-5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazoles (**13a-f**) as possible effective antimicrobial drugs.

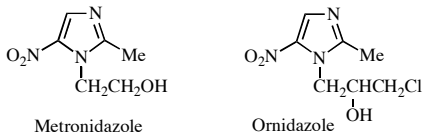


Figure 1

RESULTS AND DISCUSSION

Reaction of 2-methyl-4(5)-nitroimidazole (**1**) with ethyl α-chloroacetate suffered from poor regioselectivity (Scheme 1). In this reaction both compounds **2** and **3** were formed and the separation of compounds **2** and **3** by chromatography due to closeness of R_f value was not easy. In addition, the yields were low. Experiments were carried out to obtain improved regioselectivity of the reaction though unsuccessful. Variation of pH, temperatures and solvents affected neither the regioselectivity nor increased yields. Likewise, unsatisfactory results for N-alkylation of 4(5)-nitroimidazole were previously reported [18]. Metronidazole (**4**) was, however, commercially available. Oxidation of metronidazole using chromic acid according to the literature method gave low yield of compound **5** [19]. But oxidation of metronidazole by sodium dichromate in water to which

was slowly added sulfuric acid at ambient temperature gave the corresponding acid (**5**) in good yield (Scheme 1).

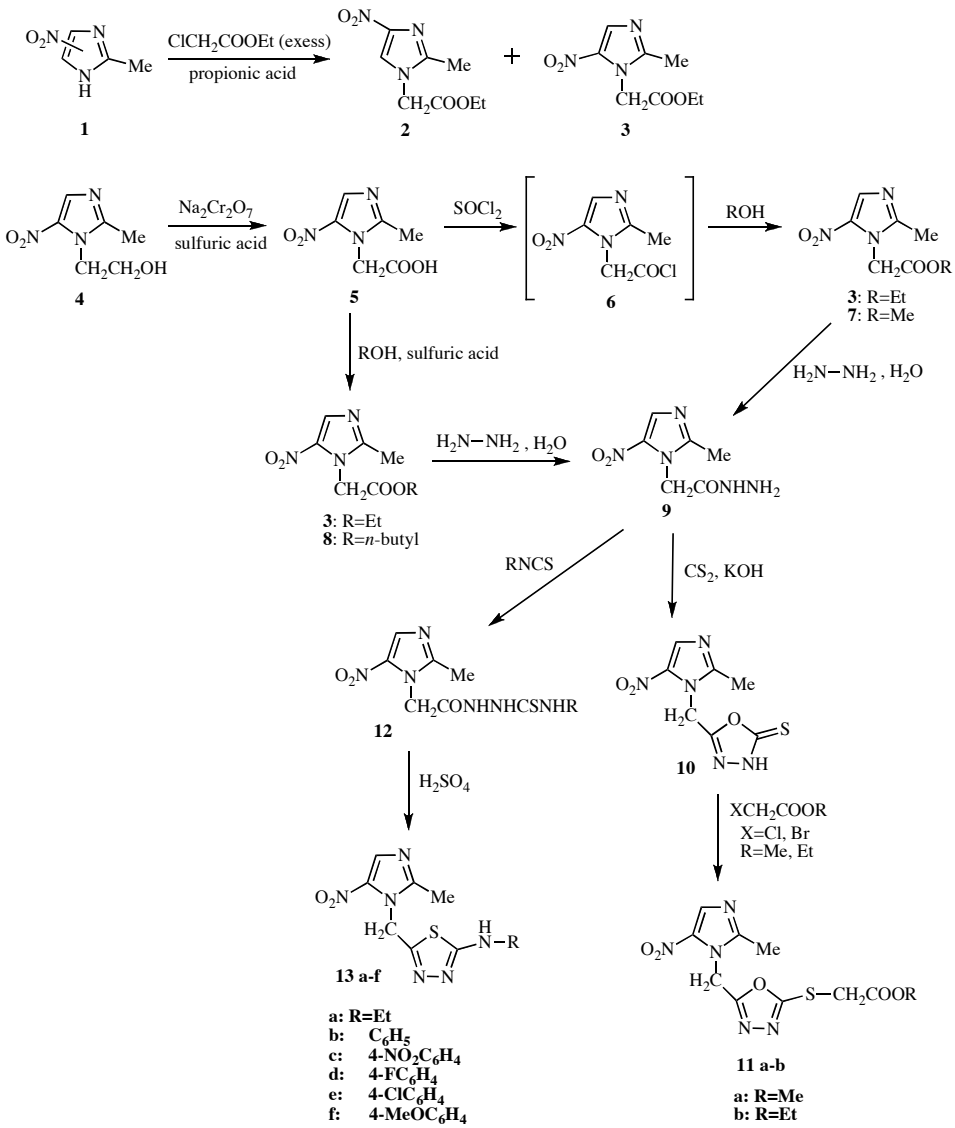
Reaction of acid **5** with thionyl chloride followed by addition of ethanol or methanol did not give good yield of corresponding ester **3** or **7**, respectively [19]. However, compound **3** was obtained by acid catalyzed esterification of acid **5** with ethanol in the presence of sulfuric acid. Reaction of hydrazine hydrate with esters **3** or **7** did not give 2-(2-methyl-5-nitro-1*H*-imidazol-1yl)acetohydrazide (**9**) in desired yield. However, compound **9** could be prepared in good yield by reacting butyl 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetate (**8**) with hydrazine hydrate.

Reaction of acid hydrazide **9** with carbon disulfide and potassium hydroxide under the modified conditions reported previously [6] afforded 5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**10**) in acceptable yield. The corresponding methyl and ethyl thioacetate derivatives **11a-b** were obtained in high yield through the reaction of compound **10** with one equivalent of methyl- or ethyl haloacetate in dioxane in the presence of potassium carbonate. Reaction of compound **9** with substituted isothiocynate yielded compound **12** [20] which was cyclized in acidic media [21] to give N-substituted 2-amino-5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-thiadiazoles (**13a-f**).

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope apparatus and are uncorrected. The FT-IR spectra were obtained using a Nicolet 550 spectrometer (Potassium bromide disks). The ^{1}H nmr spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to tetramethylsilane as the internal standard. The mass spectra were

Scheme 1



run on a Finnigan mat TSQ-70 mass spectrometer in EI mode at 70 eV. Thin layer chromatography (tlc) was performed on plates of silica gel 60 F_{254} plates. Silica gel 60, 0.040-0.063 mm (230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Most of the solvents and reagents were purchased from Merck, Aldrich and Fluka and used as such without purification.

Ethyl 2-(2-methyl-4-nitro-1*H*-imidazole-1-yl)acetate (**2**) **and ethyl 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetate** (**3**). To a suspension of 2-methyl-4(5)-nitroimidazole (**1**) [22] (2.11 g, 0.01 mol) in ethyl α-chloroacetate (14.20 mL, 0.1 mol), propionic acid (6.66 mL) was added and refluxed for 16 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether, 1:1). The fast moving fraction was compound **2** (150 mg, 7%), mp 110-111 °C (literature [23] mp 111-112 °C); ^{1}H nmr ($CDCl_3$): δ 7.75 (s, 1H, H-5 imidazole), 4.70 (s, 2H, N-CH_2), 4.27 (q, J= 7.2 Hz, 2H, -CH_2-CH_3), 2.39 (s, 3H, Me-imidazole), 1.30 (t, J=7.2 Hz, 3H, CH_3). The slower moving fraction was compound **3** (171 mg, 8%), mp 71-72 °C (literature [23] mp 71-72 °C); ^{1}H nmr ($CDCl_3$): δ 7.95 (s, 1H, H-4 imidazole), 5.02 (s, 2H, N-CH_2), 4.27 (q, J=7.2 Hz, 2H, -CH_2-CH_3), 2.45 (s, 3H, Me-imidazole), 1.30 (t, J=7.2 Hz, 3H, CH_3).

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid (**5**). To a stirring suspension of metronidazole (**4**, 85.5 g, 0.5 mol) in 200 mL H_2O at room temperature was added a solution of 142.5 g of sodium dichromate in 690 mL H_2O followed by drop wise addition of 285 mL sulfuric acid 50%. The mixture was stirred overnight. The reaction mixture was carefully neutralized with 250 mL of 4N NaOH solution. It was extracted with ethyl acetate/THF (1:1, 4×300 mL). The combined organic layer was washed with brine (1000 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue was recrystallized from CH_2Cl_2 to give 56.5 g (61%) of compound **5**, mp 176-178 °C (literature [19] mp 176-178 °C); ir (KBr): 3441 (OH), 1721 (C=O), 1547, 1357 (NO_2); ^{1}H nmr (DMSO-d_6): δ 8.10 (s, 1H, imidazole), 5.15 (s, 2H, N-CH_2), 2.42 (s, 3H, Me-imidazole); ms: m/z (%) 185 (M^+, 40), 139 (60), 109 (23), 83 (25), 80 (50), 54 (80), 52 (100).

Methyl 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetate (**7**). A solution of **5** (2.5 g, 0.01 mol) in thionyl chloride (15 mL) was refluxed for 1 h. Solvent was evaporated under reduced pressure to give crude acyl chloride **6** which without further purification was dissolved in 15 mL dry methanol and refluxed for 15 min. The reaction mixture was evaporated to dryness. To the residue water (20 mL) was added followed by addition of sodium bicarbonate solution to obtain neutral pH. The mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue was recrystallized from water to give 0.7 g (40%) of **7**, mp 139-140 °C (literature [19] mp 140 °C); ir (KBr): 1746 (C=O), 1536, 1372 (NO_2); ^{1}H nmr ($CDCl_3$): δ 7.94 (s, 1H, imidazole), 5.04 (s, 2H, N-CH_2), 3.80 (s, 3H, O-Me), 2.44 (s, 3H, Me-imidazole).

Ethyl ester of carboxylic acid **5** (compound **3**, Scheme 1) was prepared similarly from the reaction of ethanol (instead of methanol) with acyl chloride **6** in 27% yield.

Butyl 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetate (8). 2-(2-methyl-5-nitro-1H-imidazol-1-yl)acetic acid (**5**, 20 g, 0.1 mol) was suspended in 1-butanol (80 mL) and treated with 200 mL benzene and 7 mL sulfuric acid. The reaction mixture was refluxed in a Dean-Starck condenser for 4 h. The reaction solvent was partially evaporated and the residue was neutralized with aq. NaOH solution. The mixture was extracted with ethyl acetate (200 mL), dried (Na_2SO_4) and evaporated under reduced pressure. To the residue, petroleum ether was added to give a white precipitate. Recrystallization from chloroform and petroleum ether (1:9) gave compound **8** (21 g, 80%), mp 60-61 °C; ir (KBr): 1746 (C=O), 1531, 1365 (NO_2); ^{1}H nmr ($CDCl_3$): δ 7.96 (s, 1H, imidazole), 5.03 (s, 2H, N-CH_2), 4.21 (t, J=6.4 Hz, 2H, O-CH_2), 2.46 (s, 3H, Me-imidazole), 1.57-1.23 (m, 4H, CH_2-CH_2 butyl), 0.95 (t, J=6.2 Hz, 3H, CH_3 butyl); ms: m/z (%) 241 (M^+, 40), 195 (45), 185 (50), 138 (97), 108 (75), 79 (100), 54 (95). *Anal.* Calcd. for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.96; H, 5.97; N, 17.72.

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)acetohydrazide (**9**). To a stirring solution of hydrazine hydrate (6.5 mL) in an ice bath, a solution of **8** (9 g, 0.03 mol) in methanol (40 mL) was added slowly (10 min). The stirring was continued for 4.5 h at 0 °C under argon atmosphere. The white precipitate which formed in -10 °C was filtered and recrystallized from chloroform to give compound **9** (3.5 g, 60%), mp 172-174 °C; ir (KBr): 3292 (NH), 1644 (C=O), 1529, 1362 (NO_2); ^{1}H nmr (DMSO-d_6): δ 8.01 (s, 1H, imidazole) 4.94 (s, 2H, N-CH_2), 2.37 (s, 3H, Me-imidazole); ms: m/z (%) 200 (M^++1, 50), 153 (100), 125 (30), 96 (25), 84 (42), 80 (65), 53 (90). *Anal.* Calcd. for $C_6H_9N_5O_3$: C, 36.18; H, 4.55; N, 35.16. Found: C, 35.93; H, 4.37; N, 35.44.

5-[(2-Methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**10**). Compound **9** (4 g, 20.2 mmol) was suspended in 30 mL of methanol at 0 °C, potassium hydroxide (1.31 g, 20.2 mmol) and carbon disulfide (20 mL) was added. The mixture was stirred at 0 °C for 2 h, at 25 °C for another 2 h and then the mixture was refluxed for 4 h. The volatiles were evaporated under reduced pressure. Water (20 mL) was added to the residue, and the mixture was filtered. The filtrate was poured into ice and dilute HCl, and the product was collected by filtration, washed with water and recrystallized from acetic acid to give compound **10** (3.1 g, 64%), mp 205-206 °C; ir (KBr): 3452 (NH), 1536, 1378 (NO_2), 1265 (C=S); ^{1}H nmr (DMSO-d_6): δ 8.09 (s, 1H, imidazole), 5.70 (s, 2H, N-CH_2), 2.50 (s, 3H, Me-imidazole); ms: m/z (%) 241 (M^+, 15), 193 (100), 136 (20), 80 (20), 53 (30). *Anal.* Calcd. for $C_7H_7N_5O_3S$: C, 34.85; H, 2.92; N, 29.03. Found: C, 34.59; H, 3.15; N, 29.27.

Methyl 2-(5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazol-2-ylthio)acetate (**11a**). A mixture of **10** (1.4 g, 5.8 mmol) and methyl α-chloroacetate (0.62 g, 5.8 mmol) in 25 mL of dioxane was treated with 0.8 g (5.8 mmol) potassium carbonate and stirred at room temperature for 6 h. The solvent was removed under reduced pressure, water was added, and the solution was neutralized with dilute HCl and extracted with ethyl acetate (3×25 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4) and evaporated to obtain an oily residue which on purification by Silica gel flash chromatography (ethyl acetate/chloroform 1:3) afforded 0.8 g (48%) pure yellow crystals of **11a**, mp 76-77 °C; ir (KBr): 1741 (C=O), 1526, 1362 (NO_2); ^{1}H nmr ($CDCl_3$): δ 7.97 (s, 1H, imidazole), 5.75 (s, 2H, N-CH_2), 4.03 (s, 3H, O-Me), 3.78 (s, 2H, S-CH_2), 2.57 (s, 3H, Me-imidazole); ms: m/z (%) 314 (M^++1, 20), 296 (100), 267 (92), 202 (65), 187 (40), 106 (95), 73 (97), 46 (95). *Anal.* Calcd. for $C_{10}H_{11}N_5O_5S$: C, 38.34; H, 3.54; N, 22.35. Found: C, 38.12; H, 3.85; N, 22.54.

Ethyl 2-(5-[(2-methyl-5-nitro-1*H*-imidazol-1-yl)methyl]-1,3,4-oxadiazol-2-ylthio)acetate (**11b**). This compound was prepared similar to **11a** using ethyl α-bromoacetate as an oil in

69% yield, ir (KBr): 1736 (C=O), 1527, 1366 (NO_2); ^{1}H nmr ($CDCl_3$): δ 7.98 (s, 1H, imidazole), 5.76 (s, 2H, N-CH_2), 4.22 (q, J=7.1 Hz, 2H, CH_2 ethyl), 4.02 (s, 2H, S-CH_2), 2.58 (s, 3H, Me-imidazole), 1.28 (t, J=7.1 Hz, 3H, CH_3) ; ms: m/z (%) 327 (M^+, 30), 281 (60), 216 (20), 147 (20), 136 (100), 80 (50), 53 (78). *Anal*. Calcd. for $C_{11}H_{13}N_5O_5S$: C, 40.36; H, 4.00; N, 21.40. Found: C, 40.07; H, 4.32; N, 21.23.

General procedure for the preparation of N-substituted 2-amino-5-[(2-methyl-5-nitro-1*H*-imidazole-1-yl)methyl]-1,3,4-thiadiazole (13). To a solution of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetohydrazide (**9**) (1.99 g, 0.01 mol) in ethanol (20 mL) isothiocynate (0.01 mol) and sodium hydroxide (0.4 g, 0.01 mol, as a 2 *N* solution) were added. The mixture was stirred for 24 h and then filtered. The filtrate was acidified with dilute HCl in a cooled bath. The precipitate was filtered and washed with ethanol to give compound **12**. To the crude **12** (0.5 mmol) concentrated sulfuric acid (2 mL) was added and stirred for 24 h at room temperature. The reaction mixture was poured into ice and neutralized with ammonia. The precipitate was collected by filtration and recrystallized to give the desired compound **13**. The physical and spectral data of compounds **13a-f** are summarized in Table 1.

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REFERENCES

[1] Koch-Weser J.; Goldman, P. *N. Engl. J. Med*. **1980**, *303*, 1212.

[2] Ehlhardt, W. J.; Beaulieu, B. B.; Goldman, P. *J. Med. Chem*. **1988**, *31*, 323.

[3] Cosar, C.; Crisan, C.; Horclois, R.; Jacob, R. M.; Robert, J.; Tshelitsheff, S.; Vaoupre, R. *Arzneim-Forsch,* **1966**, *16*, 23.

[4] Giraldi, P.N.; Mariotti, V.; Nannini, G.; Tasolini, G. P.; Dradi, E.; Logemann, W.; de Carneri, I.; Monti, G. *Arzeim-Forsch*, **1970**, *20*, 52.

[5a] Baxter, R. A.; Spring, F. S. *J. Chem. Soc*. **1945**, 232; [b] Roe, A. M. *J.Chem. Soc*. **1963**, 2195.

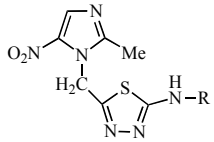
[6] Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kotlan, C. R; Schrier, D. J.; Dyer, R.D. *J. Med.Chem*. **1993**, *36*, 1090.

[7] Husain, M. I.; Kumar, A.; Srivastava, R. C. *Current Sci*. **1986**, *55*, 644.

[8] Giri, S.; Singh, H.; Yadav, L. D. S. *Agr. Biol. Chem*. **1976**, *40*, 17.

Table 1

Physical and Spectral Data of Compounds **13**



Compound	R	mp (°C)	Yield [d] %	Molecular Formula	Analysis % Calcd./Found			^{1}H nmr (DMSO-d_6)
					C	H	N	
13a	Et	160-161 [a]	70	$C_9H_{12}N_6O_2S$	40.29 40.53	4.51 4.34	31.32 31.54	8.04 (s, 1H, imidazole), 5.71 (s, 2H, N-CH_2), 3.28 (q, J=7.1 Hz, 2H, CH_2 ethyl), 2.51 (s, 3H, Me-imidazole), 1.15 (t, J=7.1 Hz, 3H, CH_3)
13b	C_6H_5	189-190 [a]	55	$C_{13}H_{12}N_6O_2S$	49.36 49.49	3.82 3.58	26.57 26.38	7.94 (s, 1H, imidazole), 7.62-6.97 (m, 5H, phenyl), 5.79 (s, 2H, N-CH_2), 2.62 (s, 3H, Me-imidazole)
13c	4-$NO_2C_6H_4$	219-220 [b]	40	$C_{13}H_{11}N_7O_4S$	43.21 42.99	3.07 3.35	27.13 27.42	8.22 (s, 1H, imidazole), 8.12 (d, J=7.6 Hz, 2H, phenyl), 7.82 (d, J=7.6 Hz, 2H, phenyl), 5.88 (s, 2H, N-CH_2), 2.55 (s, 3H, Me-imidazole)
13d	4-FC_6H_4	191-192 [c]	76	$C_{13}H_{11}N_6FO_2S$	46.70 46.44	3.32 3.01	25.14 25.42	8.06 (s, 1H, imidazole), 7.69-7.52 (m, 2H, phenyl), 7.23-7.13 (m, 2H, phenyl), 5.82 (s, 2H, N-CH_2), 2.55 (s, 3H, Me-imidazole)
13e	4-ClC_6H_4	201-203[c]	81	$C_{13}H_{11}N_6ClO_2S$	44.51 44.78	3.16 3.35	23.96 23.81	8.10 (s,1H, imidazole), 7.61 (d, J=8.9 Hz, 2H, phenyl), 7.36 (d, J=8.9 Hz, 2H, phenyl), 5.83 (s, 2H, N-CH_2), 2.53 (s, 3H, Me-imidazole)
13f	4-$MeOC_6H_4$	214-215[c]	75	$C_{14}H_{14}N_6O_3S$	48.55 48.79	4.07 4.35	24.26 24.48	7.99 (s, 1H, imidazole), 7.88-7.82 (m, 2H, phenyl), 7.58-7.50 (m, 2H, phenyl), 5.79 (s, 2H, N-CH_2), 4.10 (s, 3H, O-Me), 2.56 (s, 3H, Me-imidazole)

[a] From chloroform. [b] From water-ethanol. [c] From ethyl acetate. [d] Overall yield from **9**.

[9] Misra, H. K.; *Arch. Pharm.* **1983**, *316*, 487.

[10] Dogan, H. N.; Duron, A.; Rollas, S.; Sener, G.; Armutak, Y.; Keyer-Vysal, M. *Med. Sci. Res.* **1998**, *26*, 755.

[11] Mamolo, M. G.; Vio, L.; Banfi, E. *IL Farmaco*, **1996**, *51*, 71.

[12] Dogan, H. N.; Rollas, S.; Erdeniz, H. *IL Farmaco*, **1998**, *53*, 462.

[13] Reddy, K. R.; Mogilaiah, K.; Swamy, B.; Sreenivasul, B. *Acta Chim. Hung.* **1990**, *127*, 45.

[14] Shafiee, A.; Sayadi, A.; Hosseini Roozbahani, M.; Foroumadi, A.; Kamal, F. *Arch. Pharm. Med. Chem.* **2002**, *335*, 495.

[15] Johari Daha, F.; Matloubi, H.; Tabatabi, S. A.; Shafii, B.; Shafiee, A. *J. Heterocycl. Chem.* **2005**, *42*, 33.

[16] Shafiee, A.; Kassaee, M. Z.; Bekhradnia, A. R. *J. Heterocycl. Chem.* **2007**, *44*, 471.

[17] Eskandari, R.; Navidpour, L.; Amini, M.; Shafaroodi, H.; Shafiee, A. *J. Heterocycl. Chem.* **2007**, *44*, 449.

[18a] Gallo, G.; Pasqualucci, C. R.; Radaelli, P. *J. Org. Chem.* **1964**, *29*, 862; [b] Cox, J. S. G.; Fitzmaurioe, C.; Katritzky, A. R.; Tiddy,G. J. T. *J. Chem. Soc.* **1967**, 1251; [c] Miller, M. W.; Howes, H. L.; Kasubick, R. V.; English, A. R. *J. Med. Chem.* **1970**, *13*, 849; [d] Bhujanga, A. K. S.; Gunda, C.; Singh, B. B. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2399.

[19] Parnell, E. W. U. S. Patent 3,236,856, 1966; *Chem. Abstr.* **1966**, 64, 15893g.

[20] Shafiee, A.; Naimi, E.; Mansobi, P.; Foroumadi, A.; Shekari, M. *J. Heterocycl. Chem.* **1995**, *32*, 1235.

[21] Kress, T. J.; Costantino, S. M. *J. Heterocycl. Chem.* **1980**, *17*, 607.

[22] Fargher, R. G.; Pyman, F. L. *J. Chem. Soc.* **1919**, *115*, 217.

[23] Kajfez, F.; Sunjic, V.; Kolbah, D.; Fajdiga, T.; Oklobdzija, M. *J. Med. Chem.* **1968**, *11*, 167.