Syntheses of 1,2,4-Oxadiazole substituted Pyrazole, Isoxazole and Pyrimidine Heterocycles

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Dedicated to Professor Dr. Miha Tisler, Liubljana, on the occasion of his 70th birthday

Syntheses of two series of heterocyclic compounds having 1,2,4-oxadiazole-, together with pyrazole-, isoxazole- or pyrimidine-rings which have similar structures are reported. The mechanisms of the reactions are discussed.

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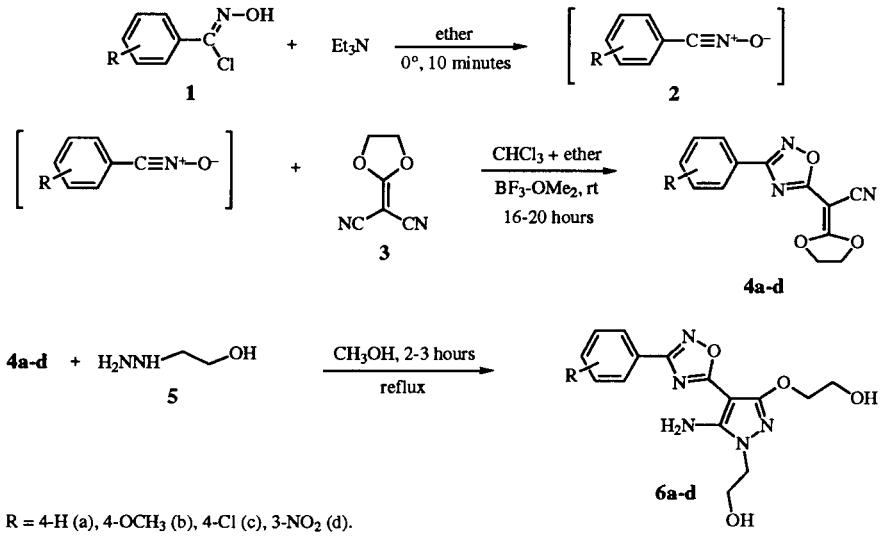
Introduction.

In relation to our previous reports about the syntheses of heterocyclic compounds from starting compounds having two cyano-groups, such as alkyl dicyanoacetates and dicyanoketene ethylene acetals [1-13], we have found that a heterocyclic compound consisting of 1,2,4-oxadiazole- as well as 1,2-pyrazole-rings can be easily prepared in two-steps reaction *via* 1,3-dipolar cycloadditions from nitrile oxides and dicyanoketene ethylene acetals [14,15] (Scheme 1).

One characteristic of the reaction is that only one CN group of the dicyanoketene ethylene acetal **3** can react with nitrile oxides **2** under our reaction conditions, no matter whether R is an electron donating (-OCH_3) or electron withdrawing (-NO_2) substituent. Perhaps the reactable CN group with a nitrile oxide must be activated by another strong electron withdrawing substituent [12]. Since the CN group is easily attacked by nucleophilic reagents, we can thus obtain a series of new heterocyclic substituted heterocycles **6a-d** through the reaction of an unreacted CN group with 2-hydroxyethylhydrazine **5**.

Scheme 1



R = 4-H (a), 4-OCH_3 (b), 4-Cl (c), 3-NO_2 (d).

Table 1

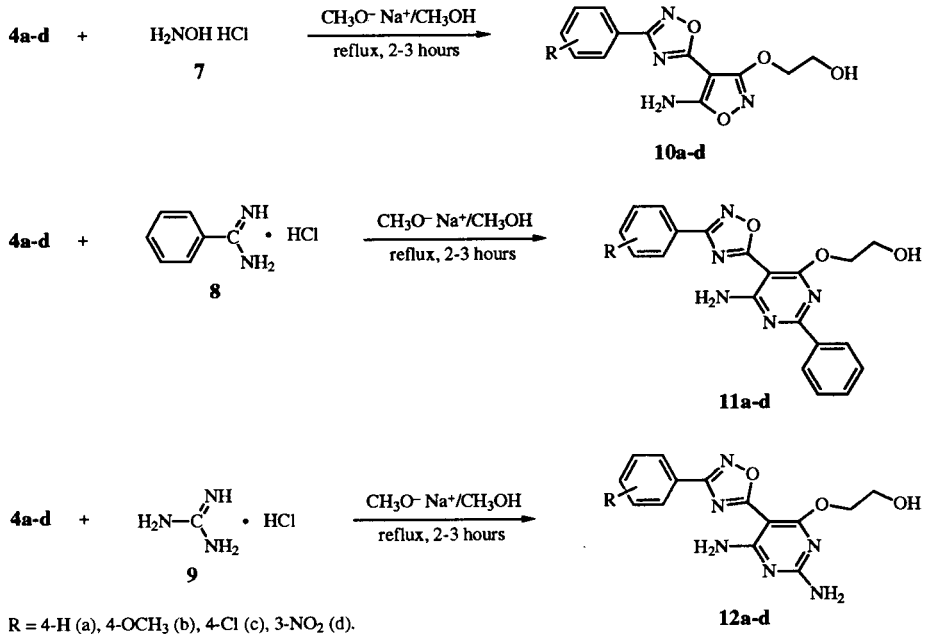
Bond Distances (in Å) of **10a**

O1' - N2'	1.442(5)	C3 - C1a	1.472(7)
O1' - C5'	1.342(6)	N4 - C5	1.300(6)
N2' - C3'	1.322(6)	C1a - C2a	1.395(7)
C3' - C4'	1.406(7)	C1a - C6a	1.382(7)
C3' - O31	1.333(5)	C2a - C3a	1.384(9)
C4' - C5'	1.373(6)	C3a - C4a	1.392(9)
C4' - C5	1.428(6)	C4a - C5a	1.354(9)
C5' - N51	1.321(7)	C5a - C6a	1.389(8)
O1 - N2	1.435(5)	O31- C32	1.444(6)
O1 - C5	1.347(5)	C32 - C33	1.473(7)
N2 - C3	1.292(6)	C33 - O34	1.399(7)
C3 - N4	1.385(6)		

The X-ray structure determination of **10a** shows that the molecule is almost in one plane (Figure 1).

These results prompted us to investigate the reactions of 1,2,4-oxadiazole dioxolanes **4a-d** with hydroxylamine **7**, amidine **8**, or guanidine **9**, which should produce the

Scheme 2



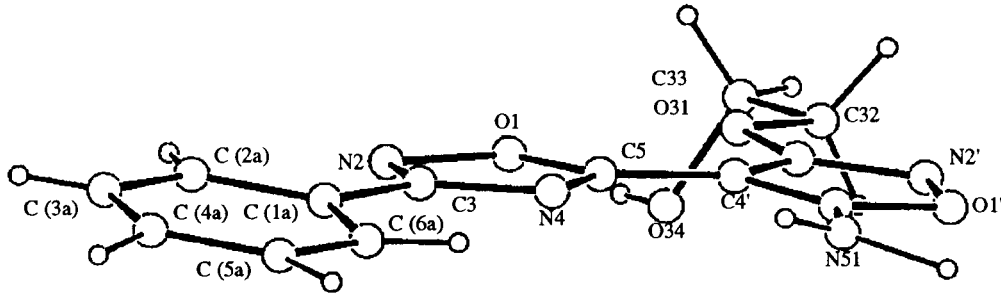


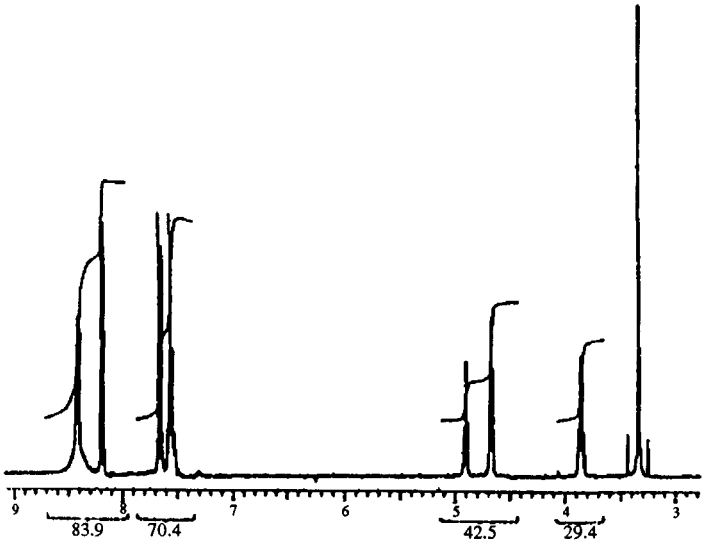
Figure 1.

expected products **10a-d**, **11a-d** and **12a-d**, according to the similar mechanism of the reaction in Scheme 1. Since one of the reagents is an amine-, amidine- or guanidine-hydrochloride salt **7**, **8** or **9**, this reaction must be carried out in the presence of a strong base such as sodium methoxide (Scheme 2). The attempts of carrying out the reaction in the presence of a weak base such as pyridine or triethylamine are unsuccessful.

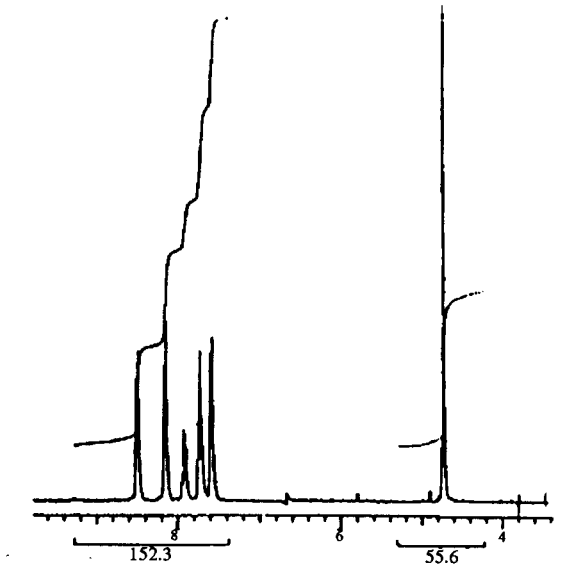
Now we have noticed an interesting phenomenon: when **4a-d** reacted with hydroxylamine hydrochloride **7**, the solution was always clear and we obtained only the expected products **10a-d**; but when **4a-d** reacted with amidine **8** or guanidine **9**, a yellow substance precipitated within the first 30 minutes under reflux. After finishing the reaction, the mixture was cooled to room temperature and filtered. The filtrate was dried and purified by column chromatography to obtain the expected products **11a-d** and **12a-d**. The residue was washed with water and dried. These yellow "by-products" are insoluble in most of the organic solvents. Mass spectra showed their molecular ion peak are always 30 fewer than the corresponding expected products. The ^{1}H- and ^{13}C-nmr spectra were measured with trifluroacetic acid as the "solvent". It showed that the signals for -CH_2CH_2OH disappeared and it had a new -CH_3 group (as shown in Scheme 3). So we suppose these "by-products" are **13a-d** and **14a-d**. The new methoxy group CH_3O- is originally from the solvent, because the sodium methoxide is a strong nucleophilic reagent. A possible mechanism of the reaction is shown in Scheme 4.

In order to prove this supposition for products **13a-d** and **14a-d**, we have tried the reaction for **11c** in two other solutions: one way is to allow the reaction in water free ethanol to reflux for 3 hours and the other is to carry out the reaction in water free ethyleneglycol at 80° for 3 hours (Scheme 5). From the first reaction we obtained besides the product **11c** also the "by-product"

Scheme 3



a. The ^{1}H-nmr spectrum of **11c** (D_6-DMSO).



b. The ^{1}H-nmr spectrum of **13c** (CF_3COOD).

Table 2

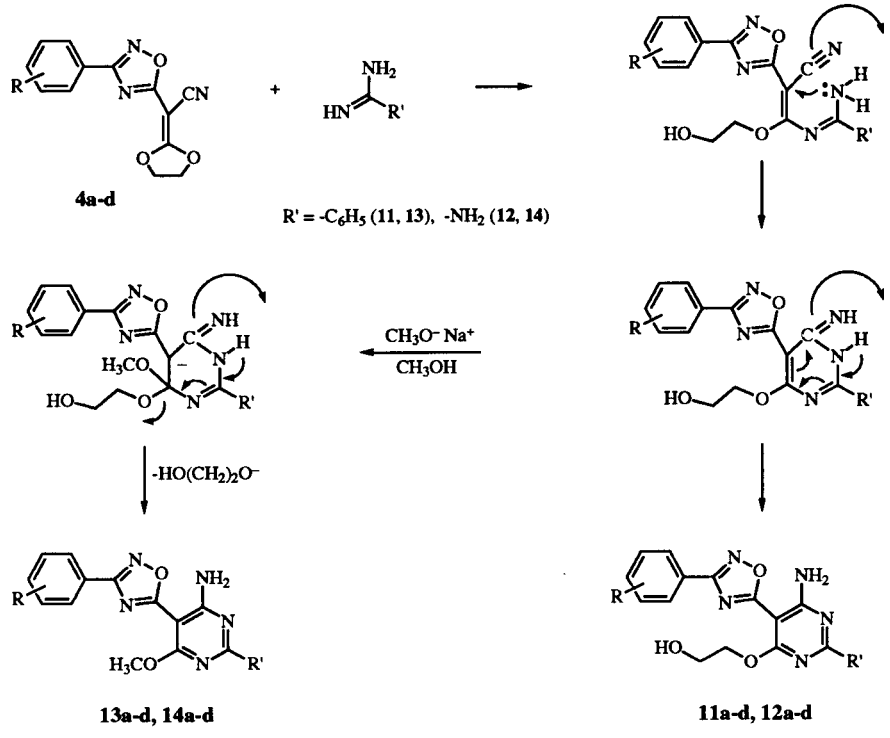
Physical and Analytical Data of the Compounds

Compound No.	mp (°C)	Yield (%)	Molecular formula Analyses
6a	181-182 (from methanol)	92	$C_{15}H_{17}N_5O_4$ Calcd. C, 54.38; H, 5.17; N, 21.14 Found C, 54.26; H, 5.19; N, 21.03
6b	179-181 (from methanol)	90	$C_{16}H_{19}N_5O_5$ Calcd. C, 53.18; H, 5.30; N, 19.38 Found C, 53.10; H, 5.29; N, 19.27
6c	186-188 (from methanol)	93	$C_{15}H_{16}N_5O_4Cl$ Calcd. C, 49.26; H, 4.41; N, 19.15 Found C, 49.26; H, 4.36; N, 19.08
6d	201-202 (from methanol)	91	$C_{15}H_{16}N_6O_6$ Calcd. C, 47.87; H, 4.28; N, 22.33 Found C, 47.79; H, 4.25; N, 22.28
10a	199-200 (acetone/ *n*-hexane)	91	$C_{13}H_{12}N_4O_4$ Calcd. C, 54.17; H, 4.20; N, 19.44 Found C, 54.16; H, 4.21; N, 19.34
10b	182-184 (acetone/ *n*-hexane)	85	$C_{14}H_{14}N_4O_5$ Calcd. C, 52.83; H, 4.43; N, 17.60 Found C, 52.73; H, 4.43; N, 17.70
10c	172-173 (acetone/ *n*-hexane)	88	$C_{13}H_{11}N_4O_4Cl$ Calcd. C, 48.39; H, 3.44; N, 17.36 Found C, 48.31; H, 3.41; N, 17.29
10d	226-228 (acetone/ *n*-hexane)	79	$C_{13}H_{11}N_5O_6$ Calcd. C, 46.85; H, 3.33; N, 21.02 Found C, 46.98; H, 3.36; N, 21.08
11a	215-217 (acetone/ *n*-hexane)	23	$C_{20}H_{17}N_5O_3$ Calcd. C, 63.99; H, 4.56; N, 18.66 Found C, 64.04; H, 4.60; N, 18.72
11b	222-223 (acetone/ *n*-hexane)	20	$C_{21}H_{19}N_5O_4$ Calcd. C, 62.22; H, 4.72; N, 17.28 Found C, 62.27; H, 4.73; N, 17.22
11c	250-252 (acetone/ *n*-hexane)	18	$C_{20}H_{16}N_5O_3Cl$ Calcd. C, 58.61; H, 3.94; N, 17.09 Found C, 58.48; H, 3.91; N, 16.99
11d	240-241 (acetone/ *n*-hexane)	16	$C_{20}H_{16}N_6O_5$ Calcd. C, 57.14; H, 3.84; N, 19.99 Found C, 56.96; H, 3.85; N, 19.94

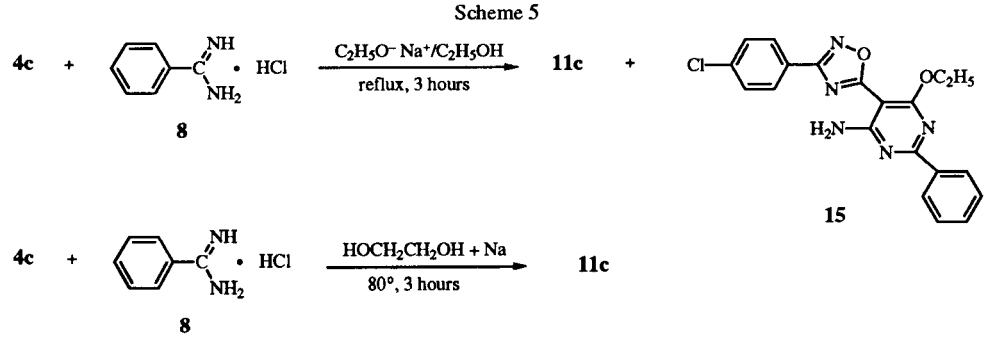
Table 2 (continued)

Compound No.	mp (°C)	Yield (%)	Molecular formula Analyses
12a	211-213 (acetone/ *n*-hexane)	17	$C_{14}H_{14}N_6O_3$ Calcd. C, 53.50; H, 4.49; N, 26.74 Found C, 53.54; H, 4.47; N, 26.68
12b	198-199 (acetone/ *n*-hexane)	17	$C_{15}H_{16}N_6O_4$ Calcd. C, 52.32; H, 4.68; N, 24.41 Found C, 52.40; H, 4.65; N, 24.37
12c	246-248 (acetone/ *n*-hexane)	17	$C_{14}H_{13}N_6O_3Cl$ Calcd. C, 48.22; H, 3.76; N, 24.10 Found C, 48.02; H, 3.77; N, 24.01
12d	253 - 255 (acetone/ *n*-hexane)	13	$C_{14}H_{13}N_7O_5$ Calcd. C, 46.80; H, 3.65; N, 27.29 Found C, 46.93; H, 3.60; N, 27.40
13a	228 - 230 extracted with ethyl acetate	62	$C_{19}H_{15}N_5O_2$ Calcd. C, 66.08; H, 4.38; N, 20.28 Found C, 66.00; H, 4.36; N, 20.21
13b	235 - 237 extracted with ethyl acetate	65	$C_{20}H_{17}N_5O_3$ Calcd. C, 63.99; H, 4.56; N, 18.66 Found C, 64.08; H, 4.59; N, 18.56
13c	236 - 238 extract with ethyl acetate	61	$C_{19}H_{14}N_5O_2Cl$ Calcd. C, 60.09; H, 3.72; N, 18.44 Found C, 60.13; H, 3.73; N, 18.35
13d	**270-** (dec.)	68	$C_{19}H_{14}N_6O_4$ Calcd. C, 58.46; H, 3.61; N, 21.53 Found C, 58.37; H, 3.64; N, 21.48
14a	226- (dec.)	69	$C_{13}H_{12}N_6O_2$ Calcd. C, 54.93; H, 4.25; N, 29.56 Found C, 54.83; H, 4.22; N, 29.48
14b	285- (dec.)	50	$C_{14}H_{14}N_6O_3$ Calcd. C, 53.50; H, 4.49; N, 26.74 Found C, 53.44; H, 4.48; N, 26.60
14c	>300 extracted with ethylacetate	58	$C_{13}H_{11}N_6O_2Cl$ Calcd. C, 48.99; H, 3.48; N, 26.37 Found C, 48.90; H, 3.47; N, 26.31
14d	>300 extracted with ethylacetate	63	$C_{13}H_{11}N_7O_4$ Calcd. C, 47.42; H, 3.37; N, 29.78 Found C, 47.34; H, 3.35; N, 29.88

Scheme 4



Scheme 5



15, which was produced due to a nucleophilic substitution of sodium ethoxide. From the second one we obtained only product **11c**, since the nucleophilic substituted product from sodium ethyleneglycol is the same as the expected product **11c**, although the yield of this reaction is very low.

Table 3

Spectroscopic Data of the Compounds

Table 3-1. IR and MS Data

Compound No.	IR ν(cm^{-1})	MS m/z (%)
6a	3650, 3405, 3310, 1685, 1620, 1560, 1165, 1080	331 (54, M$^+$), 287 (15), 170 (84), 125 (100), 77 (24), 68 (40), 45 (49)
6b	3440, 3345, 1650, 1605, 1555, 1175, 1070, 1020	361 (44, M$^+$), 317 (6), 170 (100), 138 (34), 68 (20), 45 (25)
6c	3675, 3460, 3360, 1655, 1600, 1550, 1160, 1090	367 (11.5, [M+2]$^+$), 365 (33, M$^+$), 170 (94), 125 (100), 68 (34), 45 (39)
6d	3675, 3430, 3325, 1650, 1610, 1160, 1070	376 (29, M$^+$), 333 (19), 170 (47), 138(44), 125 (100), 68 (32), 45 (46)
10a	3650, 3570, 3360, 1665, 1615, 1560, 1165, 1075	288 (16, M$^+$), 244 (11), 127 (100), 119 (27), 77 (32), 68 (14), 44 (20)
10b	3650, 3400, 3320, 1665, 1610, 1420, 1175, 1070	318 (47, M$^+$), 274 (28), 147 (100), 132 (57), 127 (76), 68 (28),44 (35)
10c	3630, 3410, 1680, 1620, 1530, 1165, 1090	324 (3, [M+2]$^+$), 322 (8.2, M$^+$), 153 (13), 127 (100), 68 (11), 45 (17)

Table 3 (continued)

Compound No.	IR ν(cm^{-1})	MS m/z (%)
10d	3450, 3340, 1665, 1610, 1530, 1270, 1170, 1090	333 (10, M$^+$), 290 (60), 190 (7), 127 (100), 76 (15), 68 (19), 45 (38)
11a	3675, 3475, 3385, 1630, 1590, 1400, 1170, 1070	375 (13, M$^+$), 331 (41), 214 (40), 104 (100), 77 (27), 68 (8), 44 (19)
11b	3675, 3475, 3310, 1650, 1610, 1590, 1180, 1060	405 (50, M$^+$), 361 (67), 214 (100), 149 (60),104 (56),77 (5), 44 (4)
11c	3675, 3470, 1650, 1630, 1575, 1370, 1160, 1090	411 (11, [M+2]+), 409 (32, M+), 365 (92), 214 (97), 104 (100), 77 (18), 44 (61)
11d	3450, 3320, 1685, 1650, 1530, 1170, 1065	420 (14, M$^+$), 376 (100), 214 (66), 104 (87), 77 (14), 68 (9), 44 (95)
12a	3455, 3395, 1650, 1615, 1560, 1490, 1165, 1070	314 (65, M$^+$), 270 (54), 153 (100), 119 (12), 77 (15), 68 (17), 43 (62)
12b	3450, 3345, 1650, 1590, 1490, 1175, 1080	344 (49, M$^+$), 300 (20), 153 (100), 149 (40), 106 (22), 86 (9), 68 (9), 43 (32)
12c	3675, 3440, 3345, 1685, 1575, 1425, 1170, 1070	350 (11, [M+2]$^+$), 348 (34, M$^+$), 304 (33), 153 (100), 137 (12), 68 (17), 43 (68)
12d	3650, 3450, 3365, 1630, 1600, 1400, 1160, 1070	359 (49, M$^+$), 315 (80), 153 (100), 137 (8), 86 (29), 68 (19), 43 (72)
13a	3630, 3470, 1620, 1590, 1400, 1170, 1105	345 (100, M$^+$), 329 (50), 118 (39), 104 (77), 77 (26), 44 (6)
13b	3540, 3365, 1620, 1590, 1415, 1150, 980	375 (100, M$^+$), 359 (72), 226 (13), 118 (43), 104 (27), 77 (19), 44 (5)
13c	3470, 3160, 1630, 1590, 1560, 1370, 1160, 1070	381 (35, [M+2]$^+$), 379 (97, M$^+$), 363 (100), 195 (16), 118 (41), 77 (14), 44 (32)
13d	3440, 3120, 1685, 1660, 1560, 1375, 1110, 1065	390 (66, M$^+$), 374 (21), 226 (12), 148 (12), 118 (100), 104 (78), 77 (35), 44 (45)
14a	3450, 3380, 1650, 1630, 1570, 1165, 1060	284 (100, M$^+$), 268 (72), 238 (26), 196 (26), 104 (51), 77 (22), 44 (8)
14b	3315, 3130, 1620, 1490, 1350, 1250, 1180, 1080	314 (75, M$^+$), 298 (100), 268 (35), 201 (5), 134 (62), 81 (7), 68 (9), 43 (12)
14c	3470, 3380, 3280, 1650, 1590, 1170, 1070	320 (3, [M+2]$^+$), 318 (10, M$^+$), 179 (4), 153 (100), 123 (6), 68 (17), 43 (68)
14d	3650, 3400, 1640, 1600, 1560, 1515, 1160, 1070	329 (100, M$^+$), 313 (47), 165 (5), 149 (20), 108 (2), 68 (13), 44 (84)

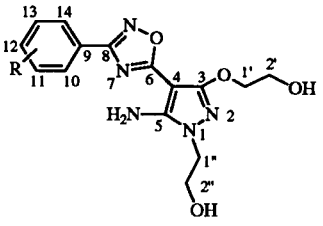
Table 3-2

^{1}H- and ^{13}C-NMR Data

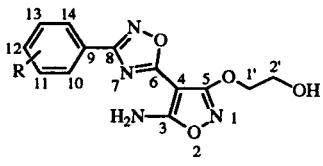
Compound No.	^{1}H-NMR δ	^{13}C-NMR δ
6a	3.65-3.75 (2q, 4H, H-2', 2"), 3.95 (t, 2H, H-1"), 4.23 (t, 2H, H-1'), 4.86, 4.96 (2t, 2H, 2OH), 6.61 (s, 2H, NH_2), 7.58 (m, 3H, arom), 8.14 (m, 2H, arom)	48.9 (+, C-1"), 59.0 (+, C-2"), 69.5 (+, C-1'), 75.9 (+, C-4), 126.5 (+, C-9), 126.9 (-, C-12), 128.7 (-, C-10, 14), 130.9 (-, C-11, 13), 149.2 (+, C-5), 158.0 (+, C-3), 166.0 (+, C-6), 170.4 (+, C-8)
6b	3.66-3.75 (m, 4H, H-2', 2"), 3.84 (s, 3H, CH_3), 3.94 (t, 2H, H-1"), 4.22 (t, 2H, H-1'), 4.85, 4.95 (2t, 2H, 2OH), 6.58 (s, 2H, NH_2), 7.10 (d, 2H, H-11, 13), 8.06 (d, 2H, H-10, 14)	48.9 (+, C-1"), 55.3 (-, CH_3), 59.0 (+, C-2"), 59.2 (+, C-2'), 69.5 (+, C-1'), 76.0 (+, C-4), 114.1 (-, C-11, 13), 118.8 (+, C-9), 128.6 (-, C-10, 14), 149.2 (+, C-5), 158.0 (+, C-3), 161.1 (+, C-12), 165.7 (+, C-6), 170.1 (+, C-8)
6c	3.67-3.78 (m, 4H, H-2', 2"), 3.94 (t, 2H, H-1"), 4.22 (t, 2H, H-1'), 4.86, 4.96 (2t, 2H, 2OH), 6.62 (s, 2H, NH_2), 7.64 (d, 2H, H-11, 13), 8.16 (d, 2H, H-10, 14)	48.9 (+, C-1"), 58.9, 59.2 (+, C-2',2"), 69.5 (+, C-1'), 75.9 (+, C-4), 125.3 (+, C-9), 128.7, 128.8 (-, C-10, 11, 13, 14), 135.6 (+, C-12), 149.3 (+, C-5), 158.0 (+, C-3), 165.2 (+, C-6), 170.5 (+, C-8)
6d	3.69-3.78 (m, 4H, H-2', 2"), 3.94 (t, 2H, H-1"), 4.22 (t, 2H, H-1'), 4.86, 4.96 (2t, 2H, OH), 6.65 (s, 2H, NH_2), 7.86 (t, 1H, H-13), 8.41, 8.57 (2m, 2H, H-12, 14), 8.80 (s, 1H, H-10)	49.01 (+, C-1"),59.04 (+, C-2"), 59.27 (+, C-2'), 69.68 (+, C-1'), 75.95 (+, C-4), 121.4 (-, C-10), 125.6 (-, C-13), 128.1 (+, C-9), 130.7 (-, C-12), 133.3 (-, C-14), 148.0 (+, C-11), 149.4 (+, C-5), 158.1 (+, C-3), 164.8 (+, C-6), 171.0 (+, C-8)
10a	3.81 (q, 2H, H-2'), 4.31 (t, 2H, H-1'), 5.00 (t, 1H, OH), 7.55-7.60 (m, 3H, H-11, 12, 13), 8.20-8.24 (m, 4H, NH_2, H-10, 14)	59.0 (+, C-2'), 71.2, 71.4 (+, C-1', 4), 126.1 (+, C-9), 127.1 (-, C-12), 128.7 (-, C-10, 14), 131.1 (-, C-11, 13), 166.4 (+, C-6), 167.7 (+, C-3), 168.6 (+, C-5), 169.8 (+, C-8)
10b	3.75 (t, 2H, H-2'), 3.83 (s, 3H, CH_3-), 4.25 (t, 2H, H-1'), 4.95 (w, 1H, OH), 7.09 (2d, 2H, H-11, 13), 8.08-8.11 (m, 4H, NH_2, H-10, 14)	55.2 (-, CH_3-), 58.91 (+, C-2'), 71.1, 71.4 (+, C-1', 4), 114.1 (-, C-11, 13), 118.4 (+, C-9), 128.8 (-, C-10, 14), 161.3 (+, C-12), 166.1 (+, C-6), 167.6 (+, C-3), 168.4 (+, C-5), 169.7 (+, C-8)
10c	3.77 (q, 2H, H-2'), 4.26 (t, 2H, H-1'), 4.97 (q, 1H, OH), 7.63 (2t, NH_2), 8.19-8.26 (m, 4H, arom)	58.7 (+, C-2'), 71.0, 71.2 (+, C-1', 4), 124.8 (+, C-9), 128.7, 128.8 (-, C-10, 11, 13, 14), 135.7 (+, C-12), 165.5 (+, C-6), 167.4 (+, C-3), 168.7 (+, C-5), 169.6 (+, C-8)
10d	3.79 (q, 2H, H-2'), 4.28 (t, 2H, H-1'), 4.99 (t, 1H, OH),7.86 (t, 1H, H-13), 8.32 (s, 2H, NH_2), 8.42 (d, 1H, H-12), 8.58 (d, 1H, H-14), 8.87 (s, 1H, H-10)	59.0 (+, C-2'), 71.3, 71.3 (+, C-1', 4), 121.7 (-, C-10), 125.8 (-, C-13), 127.9 (+, C-9), 130.7 (-, C-12), 133.4 (-, C-14), 148.2 (+, C-11), 165.4 (+, C-6), 167.8 (+, C-3), 169.5 (+, C-5), 170.0 (+, C-8)

Table 3-2 (continued)

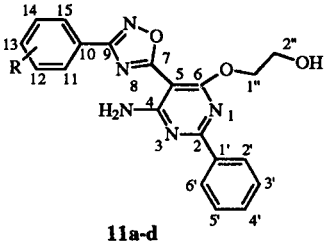
Compound No.	^{1}H-NMR δ	^{13}C-NMR δ
11a	3.88 (q, 2H, H-2"), 4.69 (t, 2H, H-1"), 4.92 (t, 1H, OH), 7.55-7.65 (m, 6H, arom), 8.17 (2d, 2H, H-11, 15), 8.40 (w, 2H, NH_2), 8.41 (2d, 2H, H-2', 6')	59.1 (+, C-2"), 68.4 (+, C-1"), 82.5 (+, C-5), 125.8 (+,C-10), 127.0, 128.0, 128.2, 128.9 (-, C-2', 4', 6', 11, 13, 15), 131.2, 131.3 (-, C-3', 5', 12, 14), 136.2 (+, C-1'), 162.6 (+, C-4), 163.3 (+, C-6), 165.8 (+, C-7), 167.5 (+, C-9), 172.5 (+, C-2)
11b	3.85 (s, 3H, CH_3-), 3.87 (q, 2H, H-2"), 4.68 (t, 2H, H-1"), 4.90 (t, 1H, OH), 7.14 (d, 2H, H-12, 14), 7.54, 7.56 (m, 3H, H-3', 4', 5'), 8.08 (d, 2H, H-11, 15), 8.40 (w, 4H, NH_2, H-2', 6')	55.2 (-, CH_3-), 59.1 (+, C-2"), 68.3 (+, C-1"), 82.5 (+, C-5), 114.3 (-, C-12, 14), 118.1 (+, C-10), 128.0, 128.2, 128.6 (-, C-2', 3', 5', 6', 11, 15), 131.2 (-, C-4'), 136.2 (+, C-1'), 161.4 (+, C-13), 162.6 (+, C-4), 163.2 (+, C-6), 165.5 (+, C-7), 167.5 (+, C-9), 172.2 (+, C-2)
11c	3.85 (q, 2H, H-2"), 4.67 (t, 2H, H-1"), 4.90 (t, 1H, OH), 7.53-7.58 (m, 3H, H-3', 4', 5'), 7.64, 7.67 (2t, 2H, H-12, 14), 8.17, 8.20 (2s, 2H, H-11, 15), 8.35-8.45 (m, 4H, NH_2, H-2', 6')	59.2 (+, C-2"), 68.5 (+, C-1"), 82.5 (+, C-5), 124.9 (+, C-10), 128.2, 128.4, 129.0, 129.2 (-, C-2', 3', 5', 6', 11, 12, 14, 15), 131.5 (-, C-4'), 136.2, 136.4 (+, C-1', 13), 162.9 (C-4), 163.7 (+, C-6), 165.4 (+, C-7), 167.8 (+, C-9), 172.9 (+, C-2)
11d	3.86 (q, 2H, H-2"), 4.67 (t, 2H, H-1"), 4.91 (t, 1H, OH), 7.52-7.57 (m, 3H, H-3', 4', 5'), 7.87 (t, 1H, H-14), 8.35-8.44 (m, 5H, NH_2, H-2', 6', 13), 8.60 (d, 1H, H-15), 8.81 (t, 1H, H-11)	59.2 (+, C-2"), 68.5 (+, C-1"), 82.4 (+, C-5), 121.5 (-, C-11), 125.8 (-, C-14), 127.4 (+, C-10), 128.1, 128.3 (-, C-2', 3', 5', 6'), 130.8 (-, C-13), 131.4 (-, C-4'), 133.3 (-, C-15), 136.2 (+, C-1'), 148.0 (+, C-12), 162.7 (+, C-4), 163.6 (+, C-6), 164.6 (+, C-7), 167.7 (+, C-9), 173.1 (+, C-2)
12a	3.76 (q, 2H, H-2'), 4.42 (t, 2H, H-1'), 4.80 (t, 1H, OH), 6.88 (s, 2H, NH_2), 7.55-7.60 (m, 4H, H-12, 13, 14, NH), 8.07 (m,2H, H-11, 15), 8.26 (w, 1H, NH)	59.3 (+, C-2'), 67.6 (+, C-1'), 76.6 (+, C-5), 126.5 (+, C-10), 127.0 (-, C-13), 129.0 (-, C-11, 15), 131.2 (-, C-12, 14), 162.5 (+, C-4), 163.6 (+, C-6), 165.5 (+, C-7), 168.4 (+, C-9), 173.7 (+, C-2)
12b	3.76 (q, 2H, H-2'), 3.84 (s, 3H, CH_3-), 4.41 (t, 2H, H-1'), 4.79 (t, 1H, OH), 6.86 (s, 2H, NH_2), 7.09 (d, 2H, H-12, 14), 7.35 (w, 1H, NH), 8.00 (d, 2H, H-11, 15), 8.15 (w, 1H, NH)	55.3 (-, CH_3-), 59.3 (+, C-2'), 67.60 (+, C-1'), 76.6 (+, C-5), 114.4 (-, C-12, 14), 118.8 (+, C-10), 128.6 (-, C-11, 15), 161.4 (+, C-13), 162.5 (+, C-4), 163.6 (+, C-6), 165.2 (+, C-7), 168.4 (+, C-9), 173.4 (+, C-2)
12c	3.75 (q, 2H, H-2'), 4.42 (t, 2H, H-1'), 4.80 (t, 1H, OH), 6.89 (s, 2H, NH_2), 7.55 (w, 1H, NH), 7.64 (d, 2H, H-12, 14), 8.10 (d, 2H, H-11, 15), 8.15 (w, 1H, NH)	59.3 (+, C-2'), 67.6 (+, C-1'), 76.5 (+, C-5), 125.3 (+, C-10), 128.8, 129.2 (-, C-11, 12, 14, 15), 135.8 (+, C-13), 162.5 (+, C-4), 163.6 (+, C-6), 164.7 (+, C-7), 168.4 (+, C-9), 173.8 (+, C-2)
12d	3.76 (q, 2H, H-2'), 4.43 (t, 2H, H-1'), 4.83 (t, 1H, OH), 6.94 (s, 2H, NH_2), 7.55 (w, 1H, NH), 7.88 (t, 1H, H-14), 8.22 (w, 1H, NH), 8.44 (2q, 1H, H-13), 8.53 (2t, 1H, H-15), 8.77 (t, 1H, H-11)	58.7 (+, C-2'), 67.2 (+, C-1'), 75.9 (+, C-5), 120.8 (-, C-11), 125.1 (-, C-14), 127.4 (+, C-10), 130.3 (-, C-13), 132.6 (-, C-15), 147.5 (+, C-12), 161.9 (+, C-7), 162.8 (+, C-4), 163.5 (+, C-6), 167.8 (+, C-9), 173.5 (+, C-2)
13a	4.76 (s, 3H, CH_3), 7.60 (t, 2H, H-3', 5'), 7.70-7.76 (m, 3H, H-12, 13, 14), 7.91 (t, 1H, H-4'), 8.14 (d, 2H, H-11, 15), 8.50 (d, 2H, H-2', 6'), NH_2 reacted with CF_3COOD	61.7 (-, CH_3), 96.6 (+, C-5), 125.6 (+, C-10), 129.1 (+, C-1'), 131.0 (-, C-12, 14), 132.2, 132.3 (-, C-2', 6', 3', 5'), 132.4 (-, C-13), 137.8 (-, C-11, 15), 140.5 (-, C-4'), 155.9, 156.3 (+, C-6, 7), 166.5 (+, C-4), 167.8 (+, C-9), 172.6 (+, C-2)
13b	3.99 (s, 3H, CH_3-), 4.73 (s, 3H, H-1"), 7.14 (d, 2H, H-12, 14), 7.73 (t, 2H, H-3', 5'), 7.92 (t, 1H, H-4'), 8.36 (d, 2H, H-11, 15), 8.48 (d, 2H, H-2', 6'), NH_2 reacted with CF_3COOD	57.3 (-, CH_3-), 61.50 (-, C-1"), 95.7 (+, C-5), 116.9 (-, C-12, 14), 121.2 (+, C-10), 129.2 (+, C-1'), 132.2, 132.3 (-, C-3', 5', 2', 6'), 137.0 (-, C-11, 15), 140.3 (-, C-4'), 156.1, 156.3 (+, C-6, 7), 163.4 (+, C-13), 167.7 (+, C-4), 168.7 (+, C-9), 172.6 (+, C-2)
13c	4.75 (s, 3H, CH_3-), 7.58 (d, 2H, H-12, 14), 7.71 (t, 2H, H-3', 5'), 7.91 (t, 1H, H-4), 8.15 (d, 2H, H-11, 15), 8.50 (d, 2H, H-2', 6'), NH_2 reacted with CF_3COOD	61.5 (-, CH_3-), 96.5 (+, C-5), 127.4 (+, C-10), 129.0 (+, C-1'), 131.4 (-, C-11, 15), 132.1, 132.2 (-, C-2', 3', 5', 6'), 134.5 (-, C-12, 14), 140.3 (-, C-4'), 145.5 (+, C-13), 155.8, 156.1 (+, C-6, 7), 165.2 (+, C-4), 167.6 (+, C-9), 172.5 (+, C-2)
13d	4.78 (s, 3H, CH_3-), 7.73 (t, 2H, H-3', 5'), 7.84, 7.92 (2q, 2H, H-4', 14), 8.52, 8.60 (2d, 4H, H-2', 6', 13, 15), 9.12 (s, 1H, H-11), NH_2 reacted with CF_3COOD	61.6 (-, CH_3-), 97.1 (+, C-5), 128.1, 128.4 (-, C-11, 13), 129.1 (+, C-1'), 130.9 (-, C-15), 131.7 (+, C-10), 132.2, 132.4 (-, C-2', 6', 3', 5'), 139.2 (-, C-14), 140.5 (-, C-4'), 149.8 (+, C-12), 155.7, 155.8 (+, C-6, 7), 163.4 (+, C-4), 167.8 (+, C-9), 172.7 (+, C-2)
14a	4.45 (s, 3H, CH_3-), 7.56 (t, 2H, H-12, 14), 7.72 (q, 1H, H-13), 8.12 (t, 2H, H-11, 15), NH_2 reacted with CF_3COOD	60.26 (-, C-1'), 91.04 (+, C-5), 128.7 (+, C-10), 130.6 (-, C-13), 132.8 (-, C-11, 15), 137.1 (-, C-12, 14), 154.9 (+, C-6), 156.6 (+, C-7), 158.9 (+, C-4), 165.2 (+, C-9), 171.2 (+, C-2)
14b	4.05 (s, 3H, CH_3-), 4.51 (s, 3H, H-1'), 7.20 (d, 2H, H-12, 14), 8.39 (d, 2H, H-11, 15), NH_2 reacted with CF_3COOD	57.1 (-, CH_3-), 60.2 (-, C-1'), 90.4 (+, C-5), 116.6 (-, C-12, 14), 121.3 (+, C-10), 136.4 (-, C-11, 15), 155.3 (+, C-7), 156.6 (+, C-6), 159.2 (+, C-4), 163.5 (+, C-13), 167.8 (+, C-9), 171.5 (+, C-2)
14c	4.52 (s, 3H, CH_3-), 7.63 (d, 2H, H-12, 14), 8.19 (d, 2H, H-11, 15), NH_2 reacted with CF_3COOD	60.6 (-, CH_3-), 91.50 (+, C-5), 127.6 (+, C-10), 131.5 (-, C-11, 15), 134.6 (-, C-12, 14), 145.4 (+, C-13), 155.5 (+, C-7), 157.0 (+, C-6), 159.5 (+, C-4), 164.6 (+, C-9), 171.6 (+, C-2)
14d	4.55 (s, 3H, CH_3-), 7.91 (t, 1H, H-14), 8.64 (2d, 2H, H-13, 15), 9.15 (s, 1H, H-11), NH_2 reacted with CF_3COOD	60.4 (-, CH_3-), 91.9 (+, C-5), 127.9 (-, C-11), 130.5 (-, C-14), 131.2 (+, C-10), 132.1 (-, C-13), 138.9 (-, C-15), 149.5 (+, C-12), 155.0 (+, C-7), 156.4 (+, C-6), 158.9 (+, C-4), 162.6 (+, C-9), 171.2 (+, C-2)



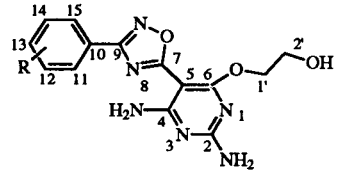
6a-d



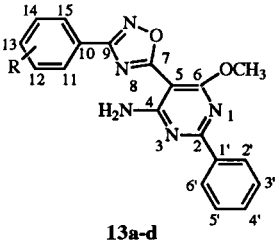
10a-d



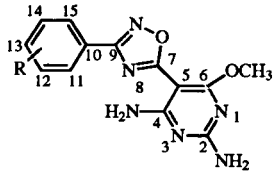
11a-d



12a-d



13a-d



14a-d

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer spectrophotometer 283 using potassium bromide and are given as cm^{-1}. ^1H- and ^{13}C-nmr spectra were recorded on either a Bruker WM-250 (^1H-nmr: 250.13 MHz, ^{13}C-nmr: 62.89 MHz) or a Varian XL 300 (^1H-nmr: 299.95 MHz, ^{13}C-nmr: 75.43 MHz) spectrometer in DMSO-d_6 or CF_3COOD. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane; coupling constants J are given in Hz. Electron impact mass spectra were obtained on a Varian MAT 311A instrument. Element analyses were performed on a Heraeus Vario EL CHNS apparatus.

General Procedure for the Preparation of 1,2,4-Oxadiazole Substituted 1,2-Pyrazole Derivates **6a-d**.

A solution of 1.10 m*M* **4a-d** and 2.00 m*M* of 2-hydroxyethyl hydrazine (**5**) in 15 ml of absolute methanol was refluxed for 2 hours. It was then cooled to -18° for 20 hours and filtered; the residue was washed with ether and recrystallized from methanol.

General Procedure for the Preparation of 1,2,4-Oxadiazole Substituted Isoxazole Derivates **10a-d**.

To a solution of 2.00 m*M* sodium in 20 ml of absolute methanol was added 2.00 m*M* of hydroxylamine hydrochloride (**7**). After 5 minutes under stirring, 1.20 m*M* of **4a-d** was added in the solution and the reaction mixture was refluxed for 2 hours. After cooling to room temperature, the solvent was evaporated and the residue was purified by column chromatography with acetone and *n*-hexane (1:1) as the eluent to give the expected products.

General Procedure for the Preparation of 1,2,4-Oxadiazole Substituted Pyrimidine Derivates **11a-d, 12a-d, 13a-d, 14a-d**.

To a solution of 2.00 m*M* of sodium in 20 ml of absolute methanol was added 2.00 m*M* of benzamidine hydrochloride **8** for **11a-d** and **13a-d** (or guanidine hydrochloride **9** for **12a-d** and **14a-d**). After 5 minutes with stirring, 1.20 m*M* of **4a-d** was added in the solution and the reaction mixture was refluxed for 3 hours. After cooling to room temperature, the mixture was filtered: the residue was washed with water, dried, and extracted with ethylacetate under reflux over 16 hours, the insoluble yellow substances are **13a-d** or **14a-d**; the solvent of the filtrate was evaporated and the residue was purified by column chromatography with acetone and *n*-hexane (1:1) as the eluent to give products **11a-d** or **12a-d**.

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