Synthesis of New Functionalized 2-Alkylsulfanyl-5-(1*H*-indol-2-yl)-1,3,4-Oxadiazole and a Facile Thio-Aza-Claisen Rearrangement of the S-Allyl Analog

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Received March 18, 2009: Revised May 05, 2009: Accepted May 05, 2009

Abstract: The S-alkylated indolyloxadiazoles **2a-l** were obtained regioselectively by alkylation of 5-(1*H*-indol-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione **1**, using TEA as acid scavenger. Alkylation of **1** with 1-bromopropane, 1-bromobutane, 1-bromoundecan, in the presence of K_2CO_3, yielded the N-alkylated products **3i-j,m** in addition to the S-alkylated analogs **2i-j**,**m**.

A facile thio-aza-Claisen rearrangement (S→N allylic rearrangement) of the S-allyl-oxadiazole **2k** to the N-allyl analog **3k** was achieved in excellent yield. Further allylation of **2k** and **3k** in the presence of K_2CO_3 led to allylation of the NH indole ring producing **5** and **6,** respectively. Benzylation of **1** in the presence of K_2CO_3 yielded **7** which resisted the S→N migration of the benzyl group. The ^{1}H NMR, ^{13}C NMR and mass spectra confirmed the structures and differentiated between the N- and S-alkylated products.

Keywords: Indoles, oxadiazoles, indolyloxadiazoles, thio-aza-Claisen rearrangement, allylic rearrangement.

INTRODUCTION

During our recent studies of the chemistry of thioglycosides [1-3], and nucleoside analogs [4], indolyl-oxadiazolethione was incorporated as the aglycon part *via* an alkylation process. The regioselectivity of the alkylation of 5-(1*H*-indol-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione **1** was studied using alkyl halides having different functionalities which could give the S- and/or N-alkyl derivatives. When the alkyl group is allyl moiety, its rearrangement from sulfur to nitrogen can be a facile method for preparing the respective N-allyl derivative. Limited reports [5-8] dealing with this phenomenon, have generally suggested that N=C-S-C-C=C gives S=C-N-C-C=C on heterocyclic systems. Allylthio-benzimidazoles [6], benzothiazolines [7], imidazolines [9], and 1,2,4-triazin-5(4*H*)-ones [5,7] have been reported to undergo thermal S→N allylic rearrangement, but 5-(allylthio)pyrimidines [10], and 8-(allylthio)caffeines [11] did not rearrange. Heating at high temperatures in a nucleophilic solvent, or in the presence of a Pd^{II}-salt as a catalyst is required for thermal rearrangement of the allylthiothiazole in bromobenzene (>265 ^oC) to give the N-allyl analog with a very low yield. However, a similar thermal rearrangement of the cinnamylthiothiazole, in a sealed tube (>265 ^oC) for several hours, led to charring [12]. With azobisisobutyronitrile (AIBN) as a radical initiator in refluxing bromobenzene (165 ^oC) 2-allylthiothiazole gave the N-allyl and the starting S-allyl in the ratio of 2:3 [13]. It is not clear, whether that rearrangement is a regular [3,3]-sigmatropic change or a non thio-Claisen type migration of the allyl moiety *via* a free radical mechanism [14]. The Pd^{II}-salt $PdCl_2(PhCN)_2$ was found to catalyze the allylic rearrangement of S-allylpyrimidine and S-allyltriazine yielding the rearranged product in a high yield [15,16]. The available synthetic methods gave low yields and were time consuming. No such rearrangement has been reported so far in the oxadiazole series. In the present work we describe an efficient high yielding method, for synthesis of the N-allyl-oxadiazole from the S-allylsulfanyl-oxadiazole.

The title heterocycles were chosen as a starting materials for the present study because of the diverse pharmacological activities of the indole [17-24] and oxadiazole derivatives [25-29] and of compounds containing both heterocycles [30-32]. The indole derivatives exhibit pharmacological activities, such as antitumor [17], anticonvulsant, tranquilizing [18], antibacterial, antifungal, antiviral [19], antiinflammatory [20], and immunosuppressive [21] activities. They are also used as physiological modulators, as inhibitors of human liver glycogen phosphorylase [22], aromatase [23], and human cytosolic phospholipase $A_2\alpha$

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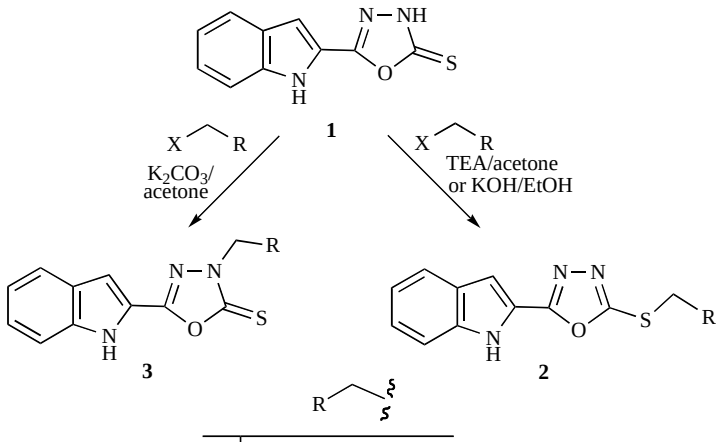
1570-1786/09 $55.00+.00



a	$-CH_2OH$
b	$-CH_2CH_2OH$
c	$-CH(OH)CH_3$
d	$-CH(OCH_2CH_3)_2$
e	-COPh
f	$-COOC(CH_3)_3$
g	-CN
h	$-COOC_2H_5$
i	$-CH_2CH_3$
j	$-CH_2CH_2CH_3$
k	$-CH=CH_2$
l	-Ph
m	$-CH_2(CH_2)_9CH_3$
n	-COOH

X= Br for all alkyl halides, except for g and h, X= Cl

Scheme 1. Synthesis of S- and N-alkylated indolyloxadiazoles.

[24]. The 1,3,4-oxadiazoles have showed anti-inflammatory, analgesic [25], antimicrobial [26], antimalarial [27], antiproliferative [28], and antituberculosis activities [29]. Heterocycles possessing indole linked to 1,3,4-oxadiazole show efficient anti-inflammatory [30,31], and antibacterial [32] activities.

RESULTS AND DISCUSSION

The thione **1** was prepared according to a reported procedure [33]. Its ^{13}C NMR spectrum showed a signal at δ_c 176.8 ppm for a C=S, and its ^1H NMR spectrum showed two singlets at δ 11.16 and 14.75 ppm corresponding to the two N-H protons. This indicates the existence of **1** in the thione rather than the thiol tautomer. Furthermore, the N-H signal at δ 11.16 ppm showed a coupling through space with a signal at δ 7.55 ppm in the NOESY-spectrum confirming its assignment to the indole N-H; other protons and carbons could be assigned by the COSY and HMQC spectra.

The thione **1** was alkylated with a set of alkyl halides in acetone containing TEA at room temperature. Only one molar equivalent of the alkyl halide was consumed by **1** giving regioselectively S-alkylated products **2a-l** in very good yields (Scheme **1**). The absence of a ^{13}C NMR signal in the range δ_c 175-177 ppm and the presence of that carbon in the range δ_c 162-164 ppm as well as the absence of the oxadiazole N-H signal in the ^1H NMR spectra of all products confirmed the assignments.

Table 1. Yields of Alkylation Products of 1

Compound	Et_3N Yield (%)	K_2CO_3 Yield (%)
2a	96	
2b	96	
2c	98	
2d	73	
2e	97	
2f	65	
2g	60	
2h	63	
2i	88	75
2j	86	79
2k	91	-
2l	90	-
2m	60	60
2n	63*	-
3i	–	25
3j	–	21
3m	40	40

*Alkylation mediated with KOH followed by acidification with HCl.

Alkylation of **1** with 1-bromopropane, 1-bromobutane and 1-bromoundecane in acetone containing K_2CO_3 gave a mixture of the N-alkylated **3i-j,m** as well as the S-alkylated derivatives **2i-j,m** (Scheme **1**). N-alkylation was deduced from the ^{13}C-NMR which showed a C=S signal in the range δc 175-176 ppm that was not in the spectra of the S-alkylated derivatives. The NH signal in the ^{1}H NMR spectra showed a long range coupling with H-7 in the NOESY spectra confirming its assignment as the indole NH. Alkylation of **1** with n-undecyl bromide in the presence of Et_3N or K_2CO_3 yielded a mixture of S- and N-alkylated oxadiazoles **2m** and **3m** in 60 % and 40 % yield respectively. Alkylation of **1** with chloroacetic acid required heating in alcoholic NaOH followed by acidification giving the acid **2n** in a moderate yield (Table **1**).

When the allylthioether **2k** was subjected to fusion under atmospheric conditions, an excellent yield of the rearranged product **3k** was obtained within 5 minutes, probably through thio-aza-Claisen rearrangement in which the allyl group migrates from sulfur to the ortho nitrogen functionality. Similarly, S,N-bis-allyl **5** gave the N,N-bis-allyl **6** in high yield. Thermal intramolecular [3,3]-sigmatropic reorganization of the allyl group from sulfur to nitrogen may take place *via* a six membered cyclic transition state **4**, in a concerted six electron reorganization, and accompanied by a rearomatization yielding the N-allyl derivative **3k**. The appearance of a ^{13}C NMR signal for C=S bond at δ_c 175 ppm, while keeping the NH ^{1}H NMR signal of the indole **3k** was strong evidence for the rearrangement. On allylation of **2k** and **3k** with allyl bromide in the presence of K_2CO_3, the NH of the indole rings were allylated to give **5** in 70 % yield and **6** in 82 % yield, respectively (Scheme **2**). Disappearance of the ^{1}H NMR signal of the NH group confirmed its allylation.

Benzylation of **1** with two molar equivalents of benzyl bromide in presence of K_2CO_3 gave **7** in moderate yield. Absence of the indole NH signal in ^{1}H NMR, and its coupling in the NOESY spectrum confirmed its benzylation (Scheme **3**). Attempted induction of the migration of the S-benzyl group in the S,N-bis-benzyl **7** by fusion failed to give **8** (Scheme **3**).

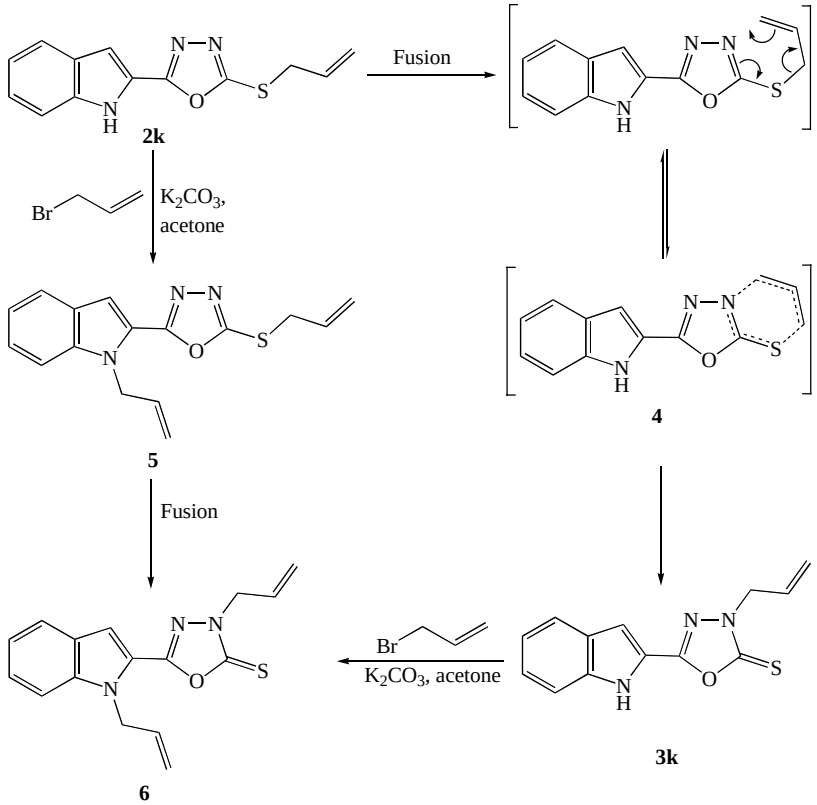
CONCLUSION

The acid scavenger required for the alkylation process played a role in directing the alkylation to the sulfur or nitrogen in 5-(1*H*-indol-2-yl)-1,3,4-oxadiazole-2(3*H*)-thione. Thio-aza Claisen rearrangement of the 2-Allylsulfanyl-5-(1*H*-indol-2-yl)-1,3,4-oxadiazole and 5-(1-allyl-1*H*-indol-2-yl)-2-allylsulfanyl-1,3,4-oxadiazole to their respective 3-N-allyl-oxadiazoles was obtained in high yield simply by their fusion. The simplicity of this rearrangement will be of potential value for further applications.

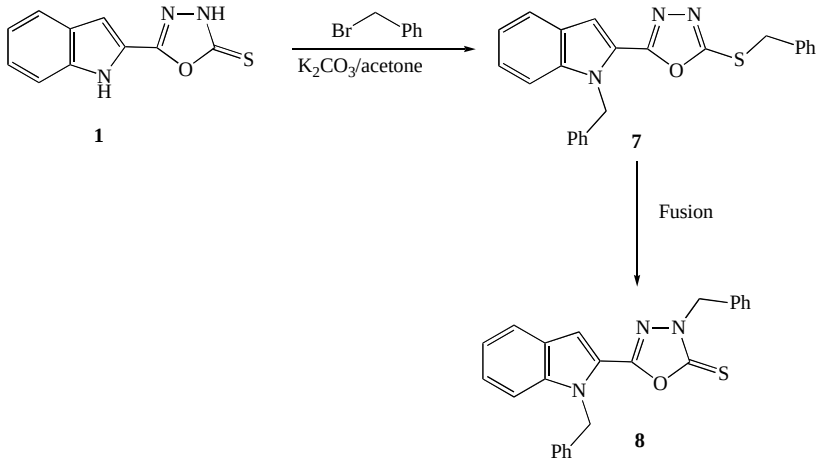
EXPERIMENTAL

General

Melting points were determined with a melt-temp apparatus (SMP10) in open capillaries and are uncorrected. TLC was performed on Merck silica gel 60 F_{254} with detection by UV light absorption. ^{1}H NMR spectra were



Scheme 2. Thio-aza-Claisen rearrangement of S-allyl and S,N-bisallyloxadiazole.



Scheme 3. Benzylation of the indolyloxadiazole thione **1**.

recorded on avane Bruker NMR spectrometer at 300 or 400 MHz, whereas the ^{13}C NMR was done on the same instrument at 75 or 100 MHz, respectively, with TMS as internal standard. Mass spectra were recorded on a Finnigan (MAT312) and Jeol (JMS.600H), HRMS were recorded with Thermo Finnegan (MAT 95XP). Solvents used were purified by simple distillation.

5-(1H-indol-2-yl)-1,3,4-oxadiazole-2(3H)-thione (1)

Recrystallized from EtOH affording yellow shining plates in 83 % yield; mp 266-268 °C (lit. [33] mp 262 °C), R_f 0.3 (9:1 $CHCl_3$/MeOH). ^1H NMR (300 MHz, DMSO-d_6): δ 7.14 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.3 Hz, H-5), 7.23 (s, 1H, H-3), 7.31 (dd, 1H, $J_{6,5}$ = 7.3, $J_{6,7}$ = 8.3 Hz, H-6), 7.54 (d, 1H, $J_{7,6}$ = 8.3 Hz, H-7), 7.71 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 11.16 (bs, 1H, indole NH, D_2O exchangeable), 14.75 (bs, 1H, oxadiazole NH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ 105.3 (C-3), 112.2 (C-7), 120.0 (C-2), 120.5 (C-$5_{ind.}$), 121.5 (C-4), 124.5 (C-6), 127.1 (C-3a), 137.8 (C-7a), 155.9 (C-$5_{oxad.}$), 176.8 (C=S). HR-EIMS: Calcd. for $C_{10}H_7N_3OS$ [M]$^+$ 217.0310; Found 217.0342.

General Procedure for synthesis of 2a-l

The appropriate alkyl halide (1.1 mmol) was added to a well stirred mixture of **1** (1.0 mmol) and Et_3N or K_2CO_3 (1.1 mmol) in dry acetone (10 ml) and stirring was continued overnight. If necessary, the mixture was filtered, washed thoroughly with acetone and acetone was evaporated in vacuo. The residue was purified by recrystallization from the appropriate solvent.

2-(2-Hydroxyeth-1-ylsulfanyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2a)

Recrystallized from EtOH/n-hexane to afford colorless crystals in 96 % yield; mp 167-169 °C, R_f 0.33 (19:1 $CHCl_3$/MeOH/). ^1H NMR (300 MHz, DMSO-d_6): δ 3.40 (t, 2H, J = 6.2 Hz, SCH_2), 3.73-3.79 (m, 2H, CH_2O), 5.16 (t, 1H, J = 5.5 Hz, OH, D_2O exchangeable), 7.09 (dd, 1H, $J_{5,4}$ = 7.9, $J_{5,6}$ = 7.3 Hz, H-5), 7.17 (s, 1H, H-3), 7.25 (dd, 1H, $J_{6,5}$ = 7.3, $J_{6,7}$ = 8.3 Hz, H-6), 7.46 (d, 1H, $J_{6,7}$ = 8.3 Hz, H-7), 7.65 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 12.2 (bs, 1H, indole NH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.2 (SCH_2), 59.4 (CH_2O), 104.8 (C-3), 112.2 (C-7), 120.3 (C-$5_{ind.}$), 120.7 (C-$2_{ind.}$), 121.4 (C-4), 124.2 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.3 (C-$5_{oxad.}$), 163.3 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{12}H_{11}N_3O_2S$ [M]$^+$ 261.0572; Found 261.0555.

2-(3-Hydroxyprop-1-ylsulfanyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2b)

Recrystallized from EtOH to afford colorless crystals in 96 % yield; mp 178-180 °C, R_f 0.36 (19:1 $CHCl_3$/MeOH). ^1H NMR (300 MHz, DMSO-d_6): δ 1.92 (m, 2H, CH_2), 3.36 (t, 2H, J = 7.1 Hz, SCH_2), 3.51-3.56 (m, 2H, CH_2O), 4.65 (t, 1H, J = 4.8 Hz, OH, D_2O exchangeable), 7.09 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.4 Hz, H-5), 7.17 (s, 1H, H-3), 7.25 (dd, 1H, $J_{5,6}$ = 7.4, $J_{6,7}$ = 8.2 Hz, H-6), 7.46 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-7), 7.65 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 12.20 (bs, 1H, indole NH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.3 (S-CH_2), 32.1 (CH_2), 58.9 (CH_2O), 104.8 (C-3), 112.2 (C-7), 120.3 (C-$5_{ind.}$), 120.7 (C-$2_{ind.}$), 121.4 (C-4), 124.2 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.3 (C-$5_{oxad.}$), 163.2 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{13}H_{13}N_3O_2S$ [M]$^+$ 275.0728; Found 275.0713.

2-(2-Hydroxyprop-1-ylsulfanyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2c)

Recrystallized from EtOH to afford colorless crystals in 98 % yield; mp 196-197 °C, R_f 0.452 (95:5 $CHCl_3$/MeOH). ^1H NMR (300 MHz, DMSO-d_6): δ 1.20 (d, 3H, J = 6.1 Hz, CH_3), 3.24 (dd, 1H, J = 13.2 Hz, J = 6.9 Hz, SCHa), 3.38 (dd, 1H, J = 13.2 Hz, J = 4.6 Hz, SCHb), 3.97-4.01 (m, 1H, CH), 5.15 (d, 1H, J = 4.9 Hz, OH, D_2O exchangeable), 7.09 (dd, 1H, $J_{5,4}$ = 7.9, $J_{5,6}$ = 7.3 Hz, H-5), 7.17 (s, 1H, H-3), 7.25 (dd, 1H, $J_{5,6}$ = 7.3, $J_{6,7}$ = 8.2 Hz, H-6), 7.46 (d, 1H, J = 8.2 Hz, H-7), 7.65 (d, 1H, J = 7.9 Hz, H-4), 12.20 (bs, 1H, indole NH, D_2O exchangeable). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.3 (CH_3), 40.7 (SCH_2), 64.8 (CH), 104.8 (C-3), 112.2 (C-7), 120.3 (C-$5_{ind.}$), 120.7 (C-2_{ind}), 121.4 (C-4), 124.2 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.3 (C-$5_{oxad.}$), 163.5 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{13}H_{13}N_3O_2S$ [M]$^+$ 275.0728; Found 275.0713.

2-(2,2-Diethoxyeth-1-ylsulfanyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2d)

Recrystallized from EtOH to afford colorless crystals in 73 % yield; mp 167-169 °C, R_f 0.27 (1:3 EtOAc/n-hexane).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 6H, J = 7.0 Hz, 2 CH_3), 3.47-3.66 (m, 6H, 3 CH_2), 4.80 (t, 1H, J = 5.1 Hz, CH), 7.09 (t, 1H, $J_{5,4}$ = 7.9, $J_{5,6}$ = 7.4 Hz, H-5), 7.18 (s, 1 H, H-3), 7.25 (dd, 1H, $J_{6,5}$ = 7.5, $J_{6,7}$ = 8.3 Hz, H-6), 7.46 (d, 1H, $J_{6,7}$ = 8.3 Hz, H-7), 7.66 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 12.2 (bs, 1H, indole NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.1 (2 CH_3), 35.4 (S-CH_2), 62.1 (2 OCH_2), 100.4 (CH), 104.9 (C-3), 112.2 (C-7), 120.3 (C-$5_{ind.}$), 120 .7 (C-$2_{ind.}$), 121.4 (C-4), 124.2 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.40 (C-$5_{oxad.}$), 162.9 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{16}H_{19}N_3O_3S$ [M]$^+$ 333.1147; Found 333.1133.

5-(1H-Indol-2-yl)-2-Phenacylsulfanyl-1,3,4-oxadiazole (2e)

Recrystallized from DMF/EtOH to afford colorless crystals in 97 % yield; mp 271-272 °C, R_f 0.79 (4:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.21 (s, 2H, SCH_2), 7.09 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.4 Hz, H-5), 7.14 (s, 1H, H-3), 7.25 (dd, 1H, $J_{6,5}$ = 7.3, $J_{6,7}$ = 8.2 Hz, H-6), 7.45 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-7), 7.59 (t, 2H, J = 8.2 Hz, Ph), 7.68 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 7.73 (t, 1H, J = 7.3 Hz, Ph), 8.08 (d, 2H, J = 7.3 Hz, Ph), 12.22 (bs, 1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.7 (SCH_2), 104.9 (C-3), 112.2 (C-7), 121.3 (C-$5_{ind.}$), 120.5 (C-$2_{ind.}$), 121.4 (C-4), 124.3 (C-6), 127.2 (C-3a), 128.5, 128.9, 134.0, 135.0 (Ph), 137.7 (C-7a), 160.4 (C-$5_{oxad.}$), 162.6 (C-$2_{oxad.}$), 192.6 (C=O). HR-EIMS: Calcd. for $C_{18}H_{13}N_3O_2S$ [M]$^+$ 335.07285; Found 335.0735.

2-(t-Butyloxycarbonylmethylsulfanyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2f)

Recrystallized from EtOH to afford colorless crystals in 65 % yield; mp 209-211 °C, R_f 0.57 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (s, 9H, 3 CH_3), 4.03 (s, 2H, SCH_2), 7.14-7.18 (m, 2H, H-3, H-5), 7.32 (dd, 1H, $J_{6,5}$ = 7.3 Hz, $J_{6,7}$ = 8.2 Hz, H-6), 7.5 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 9.3 (bs, 1H, indole NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 27.5 (3 CH_3), 34.89 (SCH_2), 82.06 [$(CH_3)_3C$], 104.9 (C-3), 112.2 (C-7), 120.4 (C-$5_{ind.}$), 120.5 (C-$2_{ind.}$), 121.5 (C-4), 124.3 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.6 (C-$5_{oxad.}$), 162.2 (C-$2_{oxad.}$), 166.6 (C=O). HR-EIMS: Calcd. for $C_{16}H_{17}N_3O_3S$ [M]$^+$ 331.0991; Found 331.0995.

2-Cyanomethylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2g)

Recrystallised from EtOH to afford colorless crystals in 60 % yield; mp 264-265 °C, R_f 0.22 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.52 (s, 2H, SCH_2), 7.10 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.3 Hz, H-5), 7.21 (s, 1H, H-3) 7.26 (dd, 1H, $J_{5,6}$ = 7.3, $J_{6,7}$ = 8.1 Hz, H-6), 7.47 (d, 1H, $J_{6,7}$ = 8.1 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 12.29 (bs, 1H, indole NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.0 (SCH_2), 105.4 (C-3), 112.3 (C-7), 116.9 (CN), 120.3 (C-$2_{ind.}$), 120.4 (C-$5_{ind.}$), 120.5 (C-2), 121.5 (C-4), 124.4 (C-6), 127.2 (C-3a), 137.8 (C-7a), 160.6 (C-$5_{oxad.}$), 161.2 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{12}H_8N_4OS$ [M]$^+$ 256.0419; Found 256.0418.

2-Ethoxycarbonylmethylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2h)

Recrystallized from EtOH to afford colorless crystals in 63 % yield; mp 177-180 °C, R_f 0.39 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 3 H, J = 7.1 Hz, CH_3), 4.12 (s, 2 H, SCH_2), 4.25 (q, 2 H, CH_2), 7.15-7.18 (m, 2 H, H-3, H-5), 7.32 (dd, 1H, $J_{5,6}$ = 7.2, $J_{6,7}$ = 8.3 Hz, H-6), 7.57 (d, 1H, $J_{6,7}$ = 8.3 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 9.72 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 34.5 (SCH_2), 62.5 (OCH_2), 106.4 (C-3), 112.1 (C-7), 120.6 (C-$2_{ind.}$), 121.0 (C-$5_{ind.}$), 121.9 (C-4), 125.7 (C-6), 127.7 (C-3a), 137.7 (C-7a), 161.1 (C-$5_{oxad.}$), 162.7 (C-$2_{oxad.}$), 167.3 (C=O). HR-EIMS: Calcd. for $C_{14}H_{13}N_3O_3S$ [M]$^+$ 303.0678; Found 303.0682.

5-(1H-Indol-2-yl)-2-Propylsulfanyl-1,3,4-oxadiazole (2i)

Recrystallized from EtOH to afford colorless crystals in 88 % yield; mp 173-175 °C, R_f 0.32 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, 3H, J = 7.3 Hz, CH_3), 1.92 (m, 2H, CH_2), 3.3 (t, 2H, J = 7.2 Hz, SCH_2), 7.15-7.18 (m, 2H, H-3, H-5), 7.31 (dd, 1H, $J_{5,4}$ = 7.9, $J_{5,6}$ = 7.1 Hz, H-6), 7.64-7.66 (m, 2H, H-4, H-7), 10.13 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.2 (CH_3), 22.8 (CH_2), 34.6 (SCH_2), 106.0 (C-3), 112.3 (C-7), 120.9 (C-$2_{ind.}$, C-$5_{ind.}$), 121.8 (C-4), 124.9 (C-6), 127.7 (C-3a), 137.7 (C-7a), 160.7 (C-$5_{oxad.}$), 164.4 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{13}H_{13}N_3OS$ [M]$^+$ 259.0779; Found 259.0796.

2-Butylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2j)

Recrystallized from EtOH to afford colorless crystals in 86 % yield; mp 178-180 °C, R_f 0.39 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, J = 7.3 Hz, CH_3), 1.47-1.55 (m, 2H, CH_2), 1.79-1.89 (m, 2H, CH_2), 3.32 (t, 2H, J = 7.3 Hz, SCH_2), 7.13-7.15 (m, 2H, H-3, H-5), 7.31 (dd, 1H, $J_{6,5}$ = 7.2, $J_{6,7}$ = 8.2 Hz, H-6), 7.57 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 9.71 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 (CH_3), 21.8 (CH_2), 31.3 (CH_2), 32.5 (SCH_2), 105.9 (C-3), 111.9 (C-7), 120.9 (C-$2_{ind.}$, C-$5_{ind.}$), 121.8 (C-4), 125.0 (C-6), 127.7 (C-3a), 137.5 (C-7a), 160.6 (C-$5_{oxad.}$), 164.4 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{14}H_{15}N_3OS$ [M]$^+$ 273.0936; Found 273.0952.

2-Allylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2k)

Recrystallized from EtOH to afford colorless needles in 91 % yield; mp 164-166 °C, R_f 0.37 (1:3 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (d, 2H, J = 6.9 Hz, SCH_2), 5.24 (d, 1H, J_{cis} = 10.0 Hz, -CH=C*H*H), 5.41 (dd, 1H, J_{trans} = 16.9 Hz, ^2J = 1.0 Hz, -CH=CH*H*), 5.97-6.08 (m, 1H, C*H*=CH_2), 7.13-7.18 (m, 2H, H-3, H-5), 7.31 (dd, 1H, $J_{6,5}$ =7.1 Hz, $J_{6,7}$ = 8.3 Hz, H-6), 7.63 (d, H, $J_{6,7}$ = 8.3 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 9.9 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.4 (SCH_2), 106.2 (C-3), 112.4 (C-7), 119.9 (-CH=*C*H$_2$), 120.7 (C-$2_{ind.}$), 120.9 (C-$5_{ind.}$), 121.7 (C-4), 125.0 (C-6), 127.7 (C-3a), 131.7 (-*C*H=CH$_2$), 137.8 (C-7a), 160.9 (C-$5_{oxad.}$), 163.4 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{13}H_{11}N_3OS$ [M]$^+$ 257.0623; Found 257.0622.

2-Benzylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2l)

Recrystallized from EtOH to afford colorless crystals in 90 % yield; mp 208-209 °C, R_f 0.40 (3:7 EtOAc/n-hexane). ^{1}H NMR (400 MHz, $CHCl_3$): δ 4.53 (s, 2H, SCH_2), 7.12 (s,1H, H-3), 7.16 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.5 Hz, H-5), 7.27-7.36 (m, 4H, H-6, Ph), 7.45 (d, 2H, J = 7.1 Hz, Ph), 7.49 (d, 1H, $J_{7,6}$ = 8.3 Hz, H-7), 7.67 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 9.3 (bs, 1H, indole NH). ^{13}C NMR (100 MHz, $CHCl_3$): δ 37.03 (SCH_2), 106.1 (C-3), 112.0 (C-7), 120.8 (C-$2_{ind.}$), 121.0 (C-$5_{ind.}$), 121.86 (C-4), 125.1 (C-6), 127.7 (C-3a), 128.20, 128.88, 129.10, 135.4, (Ph), 137.50 (C-7a),

160.78 (C-$5_{oxad.}$), 163.60 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{17}H_{13}N_3OS$ $[M]^+$ 307.0779; Found 307.0785.

5-(1H-Indol-2-yl)-2-(undec-1-ylsulfanyl)-1,3,4-oxadiazole (2m)

Yellowish white solid; 60 % yield, mp 134-136 °C R_f 0.42 (15:85 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.5 Hz, CH_3), 1.24 (bm, 14H, 7 CH_2), 1.47 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 3.31 (t, 2H, *J* = 7.4 Hz, SCH_2), 7.15 (m, 2H, H-3, H-5), 7.31 (t, 1H, *J* = 7.6 Hz, H-6), 7.55 (d, 1H, *J* = 8.2 Hz, H-7), 7.67 (d, 1H, *J* = 7.9 Hz, H-4), 9.6 (bs,1H, indole NH). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.7 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 29.3 (2 CH_2), 29.5 (CH_2), 29.6 (2 CH_2), 31.9 (CH_2), 32.8 (SCH_2), 105.9 (C-3), 111.9 (C-7), 120.96 (C-$2_{ind.}$), 120.99 (C-$5_{ind.}$), 121.8 (C-4), 125.0 (C-6), 127.8 (C-3a), 137.5 (C-7a), 160.6 (C-$5_{oxad.}$), 164.4 (C-$2_{oxad.}$). HR-EIMS: Calcd for $C_{21}H_{29}N_3OS$ $[M]^+$ 371.2031; Found 371.2033.

2-Carboxymethylsulfanyl-5-(1H-indol-2-yl)-1,3,4-oxadiazole (2n)

Chloroacetic acid (1.1 mmol) was added portionwise to a well stirred solution of **1** (1.0 mmol) in ethanolic KOH (2 N) and heated under reflux for 4 hours, then acidified by dil. HCl. The precipitate was filtered and recrystallized from ethanol to afford **2n** as colorless crystals in 63 % yield, mp 233 °C, R_f 0.19 ($CHCl_3$/EtOAc/MeOH 1:1:1.3).

^{1}H NMR (300 MHz, DMSO-d_6): δ 4.24 (s, 2H, SCH_2), 7.09 (dd, 1H, $J_{5,4}$ = 7.9, $J_{5,6}$ = 7.3 Hz, H-5), 7.22 (s,1H, H-3), 7.25 (dd, 1H, $J_{6,5}$ = 7.3, $J_{6,7}$ = 8.2 Hz, H-6), 7.46 (d, 1H, $J_{7,6}$ = 8.2 Hz, H-7), 7.66 (d, 1H, $J_{4,5}$ = 7.9 Hz, H-4), 12.24 (s,1H, indole NH), 13.2 (bs, 1H, COOH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.3 (SCH_2), 104.9 (C-3), 112.2 (C-7), 120.3 (C-$5_{ind.}$), 120.5 (C-$2_{ind.}$), 121.4 (C-4), 124.2 (C-6), 127.2 (C-3a), 137.7 (C-7a), 160.4 (C-$5_{oxad.}$), 162.4 (C-$2_{oxad.}$), 168.8 (COOH). HR-EIMS: Calcd. for $C_{12}H_9N_3O_3S$ $[M]^+$ 275.0365; Found 275.0363

Alkylation of 1 in the presence of K_2CO_3

The alkyl bromide (1.1 mmol) was added portionwise to a well stirred mixture of **1** (1.0 mmol) and K_2CO_3 (1.1 mmol), in dry acetone (10 ml) and stirring was continued overnight. The mixture was filtered, washed thoroughly with acetone and the acetone solution was evaporated in vacuo. The residues were purified by flash column chromatography (n-hexane/EtOAc 19:1).

5-(1H-Indol-2-yl)-3-Propyl-2-thioxo-1,3,4-oxadiazole (3i)

It was isolated as minor product in 25 % yield along with **2i** as a major product (75 %). Yellowish white crystals; mp 183-185 °C R_f 0.48 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, 3 H, *J* = 7.4 Hz, CH_3), 1.88-1.96 (m, 2H, CH_2), 4.08 (t, 2 H, *J* = 7.2 Hz, NCH_2), 7.15 (dd, 1H, $J_{5,4}$ = 8.0 Hz, $J_{5,6}$ = 7.1 Hz, H-5), 7.23 (s, 1H, H-3), 7.3 (dd, 1H, $J_{6,5}$ = 7.1, $J_{6,7}$ = 8.3 Hz, H-6), 7.41 (d, 1H, $J_{7,6}$ = 8.3 Hz, H-7), 7.68 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 8.68 (bs,1H, indole NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0 (CH_3), 20.9 (CH_2), 51.0 (NCH_2), 107.4 (C-3), 111.6 (C-7), 119.6 (C-2), 121.4 (C-5), 122.3 (C-4), 125.7 (C-6), 127.6 (C-3a), 137.3 (C-7a), 154.2 (C-2′), 175.7 (C=S). HR-EIMS: Calcd. for $C_{13}H_{13}N_3OS$ $[M]^+$ 259.0779; Found 259.0763.

3-Butyl-5-(1H-indol-2-yl)-2-thioxo-1,3,4-oxadiazole (3j)

It was isolated as minor product in 21 % yield along with **2j** as a major product (79 %). Yellowish white solid; mp152-154 °C R_f = 0.48 (3:7 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.0 (t, 3H, *J* = 7.3 Hz, CH_3), 1.44 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 4.11 (t, 2H, *J* = 7.2 Hz, NCH_2), 7.17 (dd, 1H, $J_{5,6}$ = 7.4 Hz, $J_{4,5}$ = 8.0 Hz, H-5), 7.21 (d, 1H, *J* = 1.4 Hz, H-3), 7.33 (dd, 1H, $J_{5,6}$ = 7.4 Hz, $J_{6,7}$ = 8.3 Hz, H-6), 7.41 (d, 1H, $J_{6,7}$ = 8.3 Hz, H-7), 7.68 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 8.68 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.7 (CH_2), 29.5 (CH_2), 49.2 (NCH_2), 107.4 (C-3), 111.5 (C-7), 119.6 (C-$2_{ind.}$), 121.4 (C-$5_{ind.}$), 122.3 (C-4), 125.7 (C-6), 127.6 (C-3a), 137.3 (C-7a), 154.2 (C-$5_{oxad.}$), 175.6 (C=S). HR-EIMS: Calcd. for $C_{14}H_{15}N_3OS$ 273.0936; Found: 273.0931.

5-(1H-Indol-2-yl)-2-thioxo-3-(undec-1-yl)-1,3,4-oxadiazole (3m)

Yellowish white solid; 40 % yield, mp 138-140 °C, R_f 0.68 (15:85 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.6 Hz, CH_3), 1.23 (bm, 16H, 8 CH_2), 1.87 (m, 2H, CH_2), 4.09 (t, 2H, *J* = 7.3 Hz, NCH_2), 7.17 (t, 1H, $J_{4,5}$ = 8.0, $J_{5,6}$ = 7.8 Hz, H-5), 7.21 (d, 1H, *J* = 1.4 Hz, H-3), 7.32 (dd, 1H, $J_{5,6}$ = 7.8, $J_{6,7}$ = 8.2 Hz, H-6), 7.41 (d, 1H, $J_{6,7}$ = 8.2 Hz, H-7), 7.68 (d, 1H, $J_{4,5}$ =8.0 Hz, H-4), 8.69 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.56 CH_2), 31.9(CH_2) 49.5 (NCH_2), 107.4 (C-3), 111.5 (C-7), 119.7 (C-$2_{ind.}$), 121.4 (C-$5_{ind.}$), 122.3 (C-4), 125.6 (C-6), 127.6 (C-3a), 137.3 (C-7a), 154.2 (C-$5_{oxad.}$), 175.6 (C=S). HR-EIMS: Calcd. for $C_{21}H_{29}N_3OS$ $[M]^+$ 371.2031; Found 371.2033.

3-Allyl-5-(1H-indol-2-yl)-2-thioxo-1,3,4-oxadiazole (3k)

Compound **2k** was fused till all the starting material converted to **3k** (5 minutes as monitored by TLC). The product was recrystallized from EtOH to afford **3k** as colorless needles in 89 % yield; mp 195-197 °C, R_f 0.49 (1:3 EtOAc/n-Hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (d, 2H, *J* = 6.1 Hz, NCH_2), 5.36-5.43 (m, 2H, -CH=CH_2), 5.90-6.37 (m, 1H, -C*H*=CH_2), 7.18 (dd, 1H, $J_{5,4}$ = 8.0, $J_{5,6}$ = 7.1 Hz, H-5), 7.22 (s, 1H, H-3), 7.33 (dd, 1H, $J_{6,5}$ = 7.1 , $J_{6,7}$ = 8.2 Hz, H-6), 7.40 (d, H, $J_{6,7}$ = 8.2 Hz, H-7), 7.62 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4), 8.7 (bs,1H, indole NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.74 (NCH_2), 107.6 (C-3), 111.6 (C-7), 119.5 (C-$2_{ind.}$), 120.6 (-CH=*C*H_2), 121.5 (C-$5_{ind.}$), 122.3 (C-4), 125.8 (C-6), 127.6 (C-3a), 129.2 (-*C*H=CH_2), 137.39 (C-7a), 154.4 (C-$5_{oxad.}$), 175.7 (C=S). HR-EIMS: Calcd. for $C_{13}H_{11}N_3OS$ $[M]^+$ 257.0623; Found: 257.0618.

5-(1-Allyl-indol-2-yl)-2-allylsulfanyl- 1,3,4-oxadiazole (5)

Allyl bromide (1.1 mmol) was added dropwise to a well stirred mixture of **2k** (1.0 mmol) and K_2CO_3 (2.0 mmol) in dry acetone (10 ml) and stirring was continued overnight. The mixture was filtered, washed thoroughly with acetone and the acetone solution was evaporated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc 8: 2) to afford **5** as a colorless oil in 70 % yield, R_f 0.58 (n-hexane/EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (d, 2H, *J* = 7.0 Hz, SCH_{2b}), 4.87 (dd, 1H, J_{trans} = 17.1 Hz, ^2J = 1.0 Hz, -C=CH_{2a}), 5.10 (dd, 1H, J_{cis} = 10.3 Hz, ^2J = 1.0 Hz, -C=CH_{2a}), 5.23 (d, 1H, *J* = 10.0 Hz,

-C=CH_{2b}), 5.33-5.35 (m, 2H, NCH_{2a}), 5.43 (dd, 1H, J_{trans} = 16.9 Hz, ^2J = 1.3 Hz, -C=CH_{2b}), 5.94-6.07 (m, 2H, –CH_a, -CH_b), 7.13-7.18 (m, 2H, H-3, H-5), 7.29-7.39 (m, 2H, H-6, H-7), 7.67 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.3 (SCH_{2b}), 47.3 (NCH_{2a}), 107.0 (C-3), 110.6 (C-7), 116.5 (=CH_{2a}), 119.9 (=CH_{2b}), 120.9 (C-$5_{ind.}$), 122.0.7 (C-4), 122.3 (C-$2_{ind.}$), 124.7 (C-6), 127.0 (C-3a), 131.7 (-CH_b), 133.2 (-CH_a), 139.0 (C-7a), 160.6 (C-$5_{oxad.}$), 163.0 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{16}H_{15}N_3OS$ [M]$^+$ 297.0936; Found 291.0923.

3-Allyl-5-(1-Allyl-indol-2-yl)-2-thioxo-1,3,4-oxadiazole (6)

Allyl bromide (1.1 mmol) was added dropwise to a well stirred mixture of **3k** (1.0 mmol) and K_2CO_3 (1.0 mmol) in dry acetone (10 ml) and stirring was continued overnight. The mixture was filtered, washed thoroughly with acetone and the acetone solution was evaporated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc 4:1) to yield **6** as colorless crystals in 82 % yield, mp 91-93 ^{o}C, R_f 0.673 (25:75 EtOAc/n-Hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (d, 2H, J = 6.0 Hz, NCH_{2c}), 4.93 (d, 1H, J_{trans} = 17.1 Hz, -C=CH_{2a}), 5.08-5.13 (m, 3H, -C=CH_{2a}, NCH_{2a}), 5.35-5.41 (m, 2H, -C=CH_{2c}), 5.87-6.02 (m, 2H, –CH_a, -CH_c), 7.17 (m, 1H, H-5), 7.29 (s, 1H, H-3), 7.35 (m, 2H, H-6, H-7), 7.67 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.3 (NCH_{2a}), 51.6 (NCH_{2c}), 108.9 (C-3), 110.4 (C-7), 116.9 (=CH_{2a}), 120.4 (=CH_{2c}),120.8 (C-$2_{ind.}$), 121.2 (C-$5_{ind.}$), 122.4 (C-4), 125.4 (C-6), 126.8 (C-3a), 129.3 (-CH_c), 132.7 (-CH_a), 139.3 (C-7a), 154.3 (C-$5_{oxad.}$), 175.2 (C=S). HRMS EI: Calcd. for $C_{16}H_{15}N_3OS$ [M]$^+$ 297.0936; Found 297.0933.

5-(1-Benzyl-indol-2-yl)-2-benzylsulfanyl-1,3,4-oxadiazole (7)

Benzyl bromide (2.1 mmol) was added to a stirred mixture of **1** (1.1 mmol) and K_2CO_3 (2.1 mmol) in dry acetone (10 ml) and stirring was continued overnight. The mixture was filtered, washed thoroughly with acetone and the acetone solution was evaporated in vacuo. The residue was purified by flash column chromatography (n-hexane/EtOAc 50:1) to afford **7** as white solid in 82 % yield mp 148-150 ^{o}C R_f = 0.66 (1:4 EtOAc/n-hexane). ^{1}H NMR (300 MHz, $CHCl_3$): δ 4.49 (s, 2H, SCH_2), 5.97 (s, 2H, NCH_2), 7.05 (d, 2H, J = 7.3 Hz, 2H-Ph), 7.14-7.25 (m, 5H, H-3, H-5, 3H-Ph), 7.28-7.36 (m, 5H, H-6, 4H-Ph), 7.41-7.44 (m, 2H , H-7, 1H-Ph), 7.69 (d, 1H, $J_{4,5}$ = 8.0 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8 (SCH_2), 48.4 (NCH_2), 107.3 (C-3), 110.8 (C-7), 120.9 (C-$5_{ind.}$), 122.0 (C-4), 122.6 (C-$2_{ind.}$), 124.9 (C-6), 126.5 (2C-Ph), 127.1 (C-3a), 127.2 (1C-Ph), 128.1 (1C-Ph), 128.5 (3C-PH), 128.8 (2C-PH), 129.1 (1C-PH), 135.4 (1 C-PH), 137.5 (C-7a), 139.3 (1C-PH), 160.6 (C-$5_{oxad.}$), 163.2 (C-$2_{oxad.}$). HR-EIMS: Calcd. for $C_{24}H_{19}N_3OS$ 397.1249; Found 397.1261.

ACKNOWLEDGEMENTS

The authors thank Prof. Dr. Atta-Ur-Rahman and Prof. Dr. M. I. Choudhary for their valuable discussions. The support from the Higher Education Commission (HEC) Pakistan (Project No. 20-697/R&D/06/38) is highly appreciated.

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