Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7539

www.rsc.org/obc

PAPER

A fast and efficient one-pot microwave assisted synthesis of variously di-substituted 1,2,4-oxadiazoles†

Andrea Porcheddu, Roberta Cadoni and Lidia De Luca*

Received 30th June 2011, Accepted 10th August 2011
DOI: 10.1039/c1ob06055d

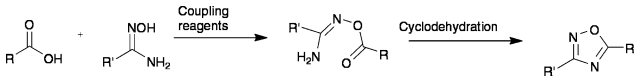
A one-pot two-step microwave assisted synthesis of variously disubstituted 1,2,4-oxadiazoles from carboxylic acids and amidoximes is reported. This methodology is characterized by short reaction times, is versatile, robust and high-yielding and allows for the preparation of heterocycles with a stereocenter with 100% enantiomeric purity.

Introduction

The 1,2,4-oxadiazole ring system is an important scaffold contained in many pharmaceutical compounds with a large spectrum of biological activities.[1] 1,2,4-Oxadiazoles have been utilized as isosteres of amides and esters due to the increased hydrolytic and metabolic stability of the ring.[2] Various 1,2,4,-oxadiazoles containing chiral α-amino acids were used in peptide mimetics, as amino acid-Gly dipeptidomimetics[3] and Phe-Gly mimetics,[4] signal transduction inhibitors,[5] and cell adhesion inhibitors.[6] 1,2,4-Oxadiazoles variously substituted in the 3,5 positions with aryl or alkyl groups have been incorporated into efficacious muscarinic agonists,[7] antirhinovirals,[8] brain-penetrant metabotropic glutamate subtype 5 (mGlu5) receptor antagonists,[9] and serotoninergic (5-HT_3) antagonists.[10] The most promising application of 1,2,4-oxadiazole framework is as potent sphingosine-1-phosphate-1 ($S1P_1$) receptor agonists[11] in the treatment of autoimmune and inflammatory disorders, multiple sclerosis, tumor metastasis and transplant rejection.

1,2,4-Oxadiazoles are generally prepared by two step procedures consisting in a condensation using amidoximes with carboxylic acid derivatives followed by an intramolecular cyclodehydration (Scheme 1).[12] The cyclization step has been carried out by the use of additives such as 1-[3-(dimethylamino)propyl]-3-ethycarbodiimide (EDC), dicyclohexylcarbodiimide (DCC), 1,1′-carbonyldiimidazole (CDI), *o*-benzotriazol-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium tetrafluoroborate (TBTU) and the Burgess reagent, employing intensive reflux conditions in DMF or pyridine.[13]

Unfortunately these approaches require very long reaction times (from 12 to 24 h) and in some cases the yields are not very high. In an effort to improve on these procedures, microwave-assisted methods have been reported.[14] Regrettably, all reported

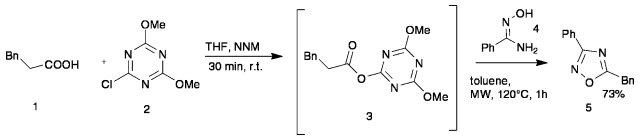


Scheme 1 Classical route to 1,2,4-oxadiazoles.

methodologies afford variable yields and do not allow access to 1,2,4-oxadiazoles with both alkyl, aryl and α-amino acids in the 3,5 positions. Besides, the majority of procedures described utilize only aryl amidoximes due to their higher reactivity compared to alkyl amidoximes.[13] Our goal was to develop a versatile, robust, high-yielding and speedy protocol for the synthesis of 1,2,4-oxadiazoles with a significant range of steric substitution patterns in 3,5 positions. Following our interest in the use of 1,3,5-triazine derivatives for the synthesis of heterocyclic compounds,[15] we have tested the possibility of using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as an activator of carboxylic acids to prepare 1,2,4-oxadiazoles.

Results and discussion

Initially our studies started with the reaction between 3-phenylpropionic acid (0.15 g, 1 mmol) **1**, CDMT (0.19 g, 1.1 mmol) **2** and *N*-methylmorpholine (NMM) (0.33 mL, 3 mmol) in THF to form quantitatively the corresponding activated ester **3** in 30 min (monitored by TLC). To this white suspension, containing the activated ester, was added phenylamidoxime (0.14 g, 1 mmol) **4** and toluene, and was heated to 120 °C for 1 h under microwave irradiation[16] (Scheme 2) to obtain the desired 5-benzyl-3-phenyl-1,2,4-oxadiazole **5** in good yield (73%).



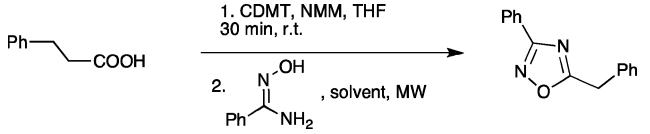
Scheme 2 Synthesis of 1,2,4-oxadiazole under microwave heating.

In order to find the optimum conditions for this synthesis various parameters, of the second step, such as solvent, temperature

Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, 07100, Sassari, Italy. E-mail: ldeluca@uniss.it; Fax: +3907922212069; Tel: +39079213529

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob06055d

Table 1 Synthesis of 1,2,4-oxadiazoles: optimization of the reaction conditions



Entry[a]	solvent	*T*/°C	Time	Yield[b] (%)
1	DMF	120	60 min	20
2	THF	120	60 min	40
3	dioxane	120	60 min	38
4	acetonitrile	120	60 min	15
5	toluene	120	60 min	72
6	toluene	150	15 min	82
7	toluene	160	5 min	93
8	toluene	170	5 min	92
9	toluene	120	60 min	10[c]
10	toluene	160	5 min	18[d]
11	toluene	160	48 h	73[e]

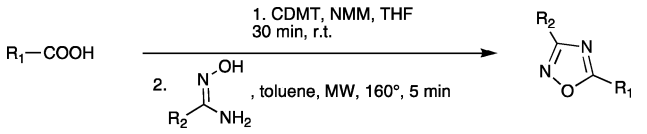
[a] *Reaction conditions*: 3-phenylpropinic acid (1.0 mmol), CDMT (1.1 mmol), and *N*-methylmorpholine (NMM) (3.0 mmol) THF (3 mL) for 30 min at r.t. Then were added phenylamidoxime (1.0 mmol) and solvent (2 mL), and heated under microwave irradiation. [b] Yield was referred to isolated product after column chromatography. [c] Reaction performed under conventional heating in a preheated oil bath at 120 °C, isolated yield after 60 min. [d] Reaction performed under conventional heating in a preheated oil bath at 160 °C, isolated yield after 5 min. [e] Reaction performed under conventional heating in a preheated oil bath at 160 °C, isolated yield after 48 h.

and time of microwave irradiation[17] were tested. Some of the most representative results are reported in Table 1. We observed very poor results when solvents such as DMF, THF, dioxane and acetonitrile were used (Table 1, entries 1–4), the best results were obtained with toluene (Table 1, entries 5–8). Temperature significantly affected the reaction, in fact the best yield was obtained irradiating the reaction mixture at 160 °C for 5 min (Table 1, entry 7), whereas at higher temperatures no appreciable increase in yield was observed (Table 1, entry 8). A comparison between conventional eating (oil bath) and microwave irradiation was carried out demonstrating a drastically better performance of the MW-assisted process (Table 1, entries 9–10).

After the optimized reaction conditions were found, we tested the methodology with an array of commercially available carboxylic acids and various substituted amidoximes[18] and the yields were satisfactory in all cases (Table 2).

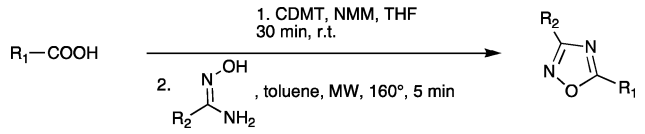
The nature of side chain did not play a significant role in terms of conversion to desired product. In the same way the procedure worked well with both aromatic and aliphatic carboxylic acids, sterically congested too (Table 2, entries 2 and 5). We should like to extend the applicability of the methodology to α-amino acids for obtaining chiral enantiomerically pure α-alkyl-5-1,2,4-oxadiazolmethanamine. Therefore the reaction was carried out with both *N*-Boc and *N*-Cbz protected α-aminoacids and we were very pleased to observe that the desired products were obtained in good yields (Table 2, entries 12, 17–23, 29, 30). It is noteworthy that the MW conditions employed are compatible with the Boc protecting group. In contrast the same reaction conducted by conventional eating (120 °C for 60 min or 160 °C for 5 min) led to the cleavage of the Boc group. Using this methodology it was also possible to prepare 1,2,4-oxadiazole-linked *N*,*N*′-orthogonally

Table 2 Carboxylic acids and amidoximes diversity



Entry	R^1	R^2	Product	Yield (%)
1	Ph-(CH2)2		5(I)	93
2	H3C, Ph		5(II)	89
3	*n*-Bu		5(III)	91
4	*n*-Bu		5(IV)	75
5			5(V)	73
6	Ph-O		5(VI)	82
7	I		5(VII)	78
8	Ph-(CH2)3	undecyl	5(VIII)	82
9		undecyl	5(IX)	79
10	Cl		5(X)	87
11			5(XI)	68

Table 2 (*Contd.*)



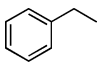
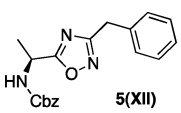
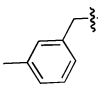
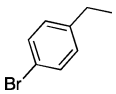
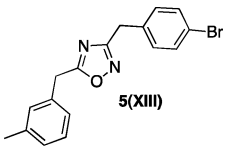
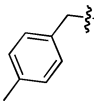
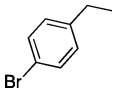
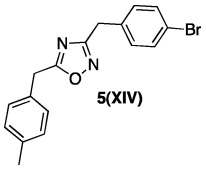
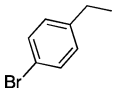
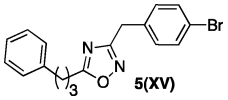
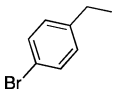
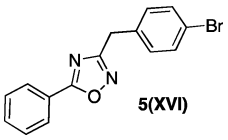
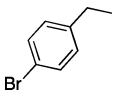
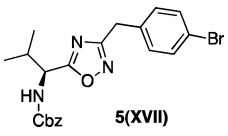
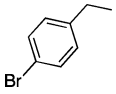
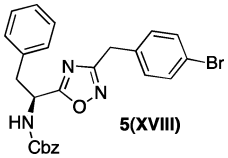
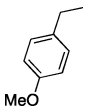
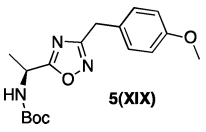
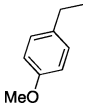
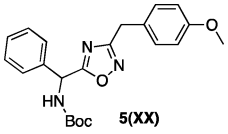
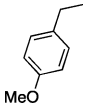
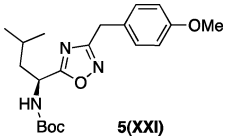
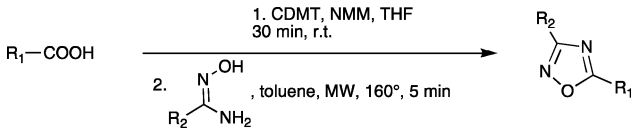
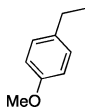
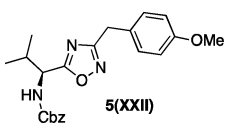
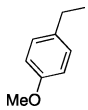
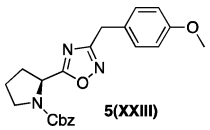
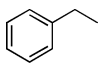
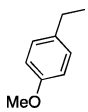
Entry	R^1	R^2	Product	Yield (%)
12			 **5(XII)**	72
13			 **5(XIII)**	87
14			 **5(XIV)**	93
15			 **5(XV)**	95
16			 **5(XVI)**	89
17			 **5(XVII)**	86
18			 **5(XVIII)**	69
19			 **5(XIX)**	72
20			 **5(XX)**	83
21			 **5(XXI)**	92

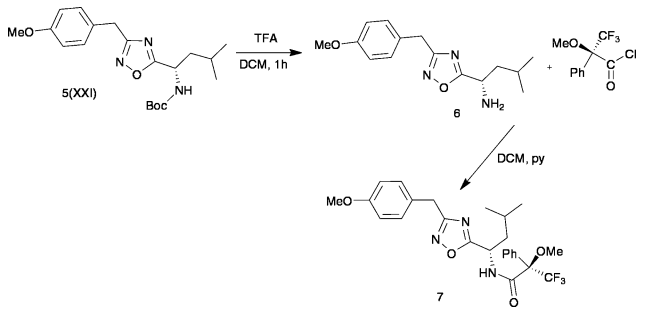
Table 2 (*Contd.*)



Entry	R^1	R^2	Product	Yield (%)
22			 **5(XXII)**	70
23			 **5(XXIII)**	76
24			**5(XXIV)**	84
25			**5(XXV)**	90
26			**3(XXVIII)**	58
27			**5(XXVII)**	62
28			**5(XXVIII)**	67
29			**5(XXIX)**	71
30			**5(XXX)**	74
31			**5(XXXI)**	65

protected dipeptidomimetic reacting *N*-Boc alanine with *N*-Cbz alanine-derived amidoxime (Table 2, entry 31). All of *N*-protected α-amino acid-derived 1,2,4-oxadiazoles were optically active. Significant racemization of the chiral center of the α-amino acids did not occur under the experimental conditions applied.

(*S*)-*tert*-butyl 1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methylbutylcarbamate **5**(XXI) was deprotected with TFA in DCM (Scheme 3) to the corresponding α-alkyl 5-1,2,4-oxadiazolemethanamine **6** (Scheme 3) which was then reacted with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MP-TACl). The enantiomeric purity of the Mosher's amide derived **7** (Scheme 3) was determined by the ^{19}F NMR and ^{1}N NMR spectra which showed it consisted of only one diastereomeric amide.



Scheme 3 Synthesis of Mosher's amide derivative.

Conclusions

It is worth remarking that by using this methodology it is possible to prepare variously disubstituted 1,2,4-oxadiazoles in a one-pot two step procedure directly from commercially available carboxylic acids and amidoximes. This method is characterized by short reaction times, is versatile, robust and high-yielding and it is also possible to prepare heterocycles with a chiral stereocenter with good chemical yields and 100% optical yield.

Experimental

General methods

All reagents and solvents were as obtained by commercial source. The *N*-Boc and *N*-Cbz derivatives of the α-amino acids were prepared according standard methods.[1]

All conventional reactions were run under dry nitrogen using standard techniques unless otherwise stated. All solvents were dried by usual methods and distilled under argon. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F254 plates and visualized using UV light at 254 nm, $FeCl_3$ (5% $FeCl_3$ in H_2O), and $KMnO_4$ staining. Microwave reactions were conducted using CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The instrument consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300W. Reactions were performed in a heavy-walled glass tubes sealed with a septum. The temperature of the content of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. After complete irradiation, the reaction tube was cooled with high-pressure air until the temperature had fallen below 35 °C. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded at 300, 75.4 and 282 MHz using $CDCl_3$ solutions and TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, d) relative to tetramethylsilane (TMS, d 0.00) or relative to residual solvent signals ($CDCl_3$, d 7.27 ppm d 2.54). Coupling constants (*J* values) are given in Hz, and peak multiplicities are denoted by s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), pd (pseudo doublet), m (multiplet), q (quartet), and t (triplet). Optical rotations were measured at ambient temperature in a 10 cm cell, and *c* is expressed in g/100 mL. Melting points were determined in open capillary tubes and are uncorrected.

General procedure for the preparation of 1,2,4-oxadiazoles 3,5-disubstitued (5(I–XXXI)).

To a stirred solution, placed in a tube (10 mL pressure-rated reaction vial), of a 3-phenylprpionic acid (0.15 g, 1 mmol) in dry THF (3 mL) was added, at room temperature, 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.19 g, 1.1 mmol) followed by *N*-methylmorpholine (0.33 mL, 3 mmol). The mixture was stirred (30–60 min) until carboxylic was consumed (monitored by TLC). Then were added phenylamidoxime (0.14 g, 1 mmol) and toluene (2 mL) and irradiated to 160 °C for 5 min in a self-tuning single mode irradiating synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 5 min. After cooling to room temperature the mixture of reaction was concentrated *in vacuo*, the residue was solubilized in EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude product was easily purified by column chromatography with hexane/EtOAc to afford 5-benzyl-3-phenyl-1,2,4-oxadiazole **5(I)** as pale yellow oil in good yield (0.23 g, 93%). R_f 0.37 (hexane/EtOAc: 90/10). (Found: C, 76.76; H, 5.76; N, 11.07. Calc for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19).). ν_{max}/cm^{-1} 3063, 3028, 2924, 2849, 1727, 1593, 1570, 1528, 1446. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07 (m, 2H); 7.48 (m, 3H); 7.27 (m, 5H); 3.23 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.9; 168.3; 139.4; 131.1; 128.8; 128.7; 128.2; 127.4; 126.7; 114.0; 32.6; 28.5. MS *m*/*z* 251 (M+H).

3-Phenyl-5-(1-phenylethyl)-1,2,4-oxadiazole 5(II)

Yield (0.22 g, 89%). Pale yellow oil. R_f 0.35 (hexane/EtOAc: 90/10). (Found: C, 76.74; H, 5.71; N, 11.10. Calc. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19). ν_{max}/cm^{-1} 3067, 3035, 2923, 2847, 1732, 1597, 1572, 1530. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (m, 2H); 7.32 (m, 8H); 7.27 (q, *J* = 7.2 Hz, 1H); 1.79 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.9; 168.3; 139.4; 131.1; 128.8; 128.7; 128.2; 127.4; 126.7; 114.0; 32.6; 28.5. MS *m*/*z* 251 (M+H).

5-butyl-3-phenyl-1,2,4-oxadiazole 5(III)

Yield (0.18 g, 91%). Pale yellow oil. R_f 0.79 (hexane/EtOAc: 90/10). (Found: C, 71.24; H, 6.95; N, 13.93. Calc. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85).). ν_{max}/cm^{-1} 3071, 3036, 2960 2934, 2873, 1594, 1570, 1446.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08 (m, 2H); 7.49 (m, 3H); 2.95 (t, *J* = 7.7 Hz, 2H); 1.86 (m, 2H); 1.46 (m, 2H); 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.9; 168.1; 130.8; 128.6; 127.4; 126.9; 28.5; 26.1; 22.0; 13.4. MS *m*/*z* 203 (M+H).

5-butyl-3-*o*-tolyl-1,2,4-oxadiazole 5(IV)

Yield (0.16 g, 75%). Pale yellow oil. R_f 0.62 (hexane/EtOAc: 95/5). (Found: C, 72.21; H, 7.48; N, 12.91. Calc. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95).). ν_{max}/cm^{-1} 3064, 2960, 2932, 2873, 1591, 1569. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.97 (m, 1H); 7.34 (m, 3H); 2.95(t, J = 7.5 Hz, 2H); 2.62 (s, 3H), 1.84(m, 2H); 1.45 (m, 2H); 0.97 (t, J = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.9; 168.7; 138.1; 131.2; 130.3; 129.9; 126.2; 125.8; 28.6; 26.1; 22.1; 22.0; 13.5. MS m/z 217 (M+H).

5-neopentyl-3-*o*-tolyl-1,2,4-oxadiazole 5(V)

Yield (0.18 g, 73%). Pale yellow oil. R_f 0.65 (hexane/EtOAc: 95/5). (Found: C, 72.98; H, 7.89; N, 12.13. Calc. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16).). ν_{max}/cm^{-1} 3063, 2961, 2869, 1590, 1568.^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.99 (d, J = 8.8 Hz, 1H); 7.33 (m, 3H); 2.86 (s, 2H); 2.63 (s, 3H); 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.4; 168.7; 138.1; 131.3; 130.4; 130.0; 125.9; 114.0; 40.1; 31.9; 29.4; 22.1. MS m/z 231 (M+H).

5-(phenoxymethyl)-3-*o*-tolyl-1,2,4-oxadiazole 5(VI)

Yield (0.22 g, 82%). Pale yellow oil. R_f 0.31 (hexane/EtOAc: 95/5). (Found: C, 72.11; H, 5.32; N, 10.48. Calc for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52). ν_{max}/cm^{-1} 3060, 2960, 2926, 2855, 1723, 1589, 1495.^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00 (d, J = 7.2 Hz, 1H); 7.33 (m, 5H); 7.04 (m, 3H); 5.36 (s, 2H); 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.7; 157.6; 138.3; 131.4; 130.7; 130.2; 129.7; 126.0; 122.3; 114.9; 112.4; 107.5; 61.1; 22.1. MS m/z 267 (M+H).

5-(2-iodophenyl)-3-*o*-tolyl-1,2,4-oxadiazole 5(VII)

Yield (0.28 g, 78%). Yellow solid. mp 63-53 °C. R_f 0.51 (hexane/EtOAc: 95/5). (Found: C, 49.78; H, 3.03; N, 7.59. Calc for $C_{15}H_{11}IN_2O$: C, 49.75; H, 3.06; N, 7.73). ν_{max}/cm^{-1} 2923, 2851, 1725, 1596, 1567, 1455. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.12 (d, J = 6.4 Hz, 2H); 8.02 (d, J = 7.9 Hz, 1H); 7.53 (t, J = 7.5 Hz, 1H); 7.37 (m, 3H); 7.26 (m, 1H); 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.4; 169.2; 161.3; 141.7; 138.4; 132.9; 131.6; 131.4; 130.7; 130.2; 129.4; 128.3; 126.0; 94.6; 22.3. MS m/z 363 (M+H).

5-(3-phenylpropyl)-3-undecyl-1,2,4-oxadiazole 5(VIII)

Yield (0.28 g, 82%). Pale yellow oil. R_f 0.73 (hexane/EtOAc: 90/10). (Found: C, 77.16; H, 9.96; N, 8.13. Calc for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; N, 8.18). ν_{max}/cm^{-1} 3063, 3027, 2926, 2855, 1603, 1584, 1496, 1454. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.20 (m, 5H); 4.10 (q, J = 8.4 Hz, 2H); 2.63 (t, J = 7.7 Hz, 2H); 2.28 (q, J = 7.5 Hz, 4H); 1.94 (m, 2H); 1.51 (m, 3H); 1.25 (m, 14H); 0.88 (t, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.1; 141.2; 128.2; 128.1; 125.7; 119.5; 59.9; 34.9; 33.3; 31.7; 29.3; 29.2; 29.1; 28.5; 28.4; 26.3; 25.1; 22.4; 16.8; 13.9. MS m/z 343 (M+H).

5-*m*-tolyl-3-undecyl-1,2,4-oxadiazole 5(IX)

Yield (0.25 g, 79%). Pale yellow oil. R_f 0.74 (hexane/EtOAc: 90/10). (Found: C, 76.41; H, 9.93; N, 8.88. Calc for $C_{20}H_{30}N_2O$: C, 76.39; H, 9.62; N, 8.91). ν_{max}/cm^{-1} 3056, 2924, 2854, 1568, 1456. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.86 (m, 2H); 7.34 (m, 2H); 4.19 (q, J = 7.1 Hz, 2H); 4.12 (q, J = 7.1 Hz, 1H); 2.40 (s, 3H); 2.28 (t, J = 7.5 Hz, 1H); 2.17 (s, 1H); 1.64 (m, 2H); 1.40 (t, J = 8.1 Hz, 4H); 1.25 (m, 10H); 0.88 (t, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4; 137.7; 133.2; 129.8; 127.9; 126.4; 124.9; 119.5; 60.5; 31.7; 29.3; 29.1; 28.5; 28.4; 25.1; 22.4; 21.0; 16.8; 14.0; 13.8. MS m/z 315 (M+H).

5-(4-chlorophenyl)-3-cyclohexyl-1,2,4-oxadiazole 5(X)

Yield (0.23 g, 87%). Yellow solid. mp 107-110 °C. R_f 0.61 (hexane/Et_2O: 95/5). (Found: C, 63.89; H, 5.76; N, 10.67. Calc for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66). ν_{max}/cm^{-1} 3032, 2926, 2857, 1608, 1583, 1509, 1479. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (d, J = 8.5 Hz, 2H); 7.49 (d, 8.5 Hz, 2H); 2.86 (m, 1H); 2.06 (m, 2H); 1.88 (m, 2H); 1.64 (m, 2H); 1.37 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.1; 174.4; 139.1; 129.6; 129.5; 123.2; 36.2; 30.9; 26.0; 25.9. MS m/z 263 (M+H).

3,5-dibenzyl-1,2,4-oxadiazole 5(XI)

Yield (0.17 g, 68%). Pale yellow oil. R_f 0.31 (hexane/Et_2O: 78/0.2). (Found: C, 76.75; H, 5.66; N, 11.16. Calc for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19). ν_{max}/cm^{-1} 3088, 3064, 3031, 2927, 1676, 1576, 1496. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (m, 10H); 4.17 (s, 2H); 4.04 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.9; 169.5; 135.4; 133.4; 129.0; 128.9; 128.8; 128.6; 127.5; 127.0; 32.9; 32.3. MS m/z 251 (M+H).

(*S*)-benzyl 1-(3-benzyl-1,2,4-oxadiazol-5-yl)ethylcarbamate 5(XII)

Yield (0.17 g, 72%). Pale yellow oil. $[\alpha]_D^{20}$ −36.7 (c 0.30 in DCM). R_f 0.60 (hexane/EtOAc: 60/40). (Found: C, 67.61; H, 5.63; N, 12.16. Calc for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46). ν_{max}/cm^{-1} 3323, 3088, 3064, 3032, 2986, 2952, 1722 (C═O), 1578, 1525, 1455. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32 (m, 10H); 5.52 (m, 1H); 5.10 (m, 2H); 4.04 (s, 2H); 1.54 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.5; 169.3; 159.3; 135.1; 128.9; 128.6; 128.5; 128.2; 128.1; 127.1; 126.9; 67.2; 44.6; 32.2; 19.9. MS m/z 238 (M+H).

3-(4-bromobenzyl)-5-(3-methylbenzyl)-1,2,4-oxadiazole 5(XIII)

Yield (0.30 g, 87%). Pale yellow oil. R_f 0.58 (hexane/EtOAc: 90/10). (Found: C, 59.51; H, 4.44; N, 8.12. Calc for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41; N, 8.16). ν_{max}/cm^{-1} 3027, 2920, 1578, 1488. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 (m, 2H); 7.17 (m, 6H); 4.14 (s, 2H); 3.99 (s, 2H); 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.3; 169.0; 138.6; 134.3; 133.1; 131.7; 130.7; 129.6; 128.8; 128.3; 125.8; 121.1; 32.9; 31.7; 21.3. MS m/z 343 (M+H).

3-(4-bromobenzyl)-5-(4-methylbenzyl)-1,2,4-oxadiazole 5(XIV)

Yield (0.32 g, 93%). Pale yellow solid. mp 71–74 °C. R_f 0.71 (hexane/EtOAc: 80/20). (Found: C, 59.47; H, 4.46; N, 8.14. Calc for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41; N, 8.16). ν_{max}/cm^{-1} 3024, 2917, 1587, 1513, 1489.^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 8.4 Hz, 2H); 7.16 (m, 6H); 4.13 (s, 2H); 3.98 (s, 2H); 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.4; 169.0; 137.3; 134.3; 131.7; 130.7; 130.2; 129.5; 128.7; 121.1; 32.5; 31.7; 21.0. MS m/z 343 (M+H).

3-(4-bromobenzyl)-5-(3-phenylpropyl)-1,2,4-oxadiazole 5(XV)

Yield (0.34 g, 95%). Pale yellow oil. R_f 0.29 (hexane/EtOAc: 90/10). (Found: C, 60.49; H, 4.76; N, 7.85. Calc for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84). ν_{max}/cm^{-1} 3084, 3061, 3026, 2927, 2858, 1579, 1489.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.43 (d, J = 8.3 Hz, 2H); 7.21 (m, 7H); 3.98 (s, 2H); 2.83 (t, J = 7.2 Hz, 2H); 2.68 (t, J = 7.5 Hz, 2H); 2.1 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.8; 168.8; 140.5; 135.1; 134.4; 131.7; 130.6; 128.4; 126.1; 121.1; 34.8; 31.7; 27.9; 25.8. MS m/z 357 (M+H).

3-(4-bromobenzyl)-5-phenyl-1,2,4-oxadiazole 5(XVI)

Yield (0.28 g, 89%). Pale yellow solid. mp 76–78 °C. R_f 0.30 (hexane/Et_2O: 95/5). (Found: C, 57.08; H, 3.54; N, 8.85. Calc for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89). ν_{max}/cm^{-1} 2930, 1721, 1607, 1560, 1486. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (d, J = 6.9 Hz, 2H); 7.51 (m, 5H); 7.26 (d, J = 8.3 Hz, 2H); 4.09 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.79; 169.5; 134.4; 132.7; 131.7; 130.7; 128.9; 128.0; 124.0; 121.0; 31.8. MS m/z 315 (M+H).

(*S*)-benzyl 1-(3-(4-bromobenzyl)-1,2,4-oxadiazol-5-yl)-2-methylpropylcarbamate 5(XVII)

Yield (0.38, 86%). Pale yellow solid. mp 69–71 °C. $[\alpha]_D^{20}$ −61.3 (c 0.42 in DCM). R_f 0.23 (hexane/EtOAc: 90/10). (Found: C, 56.80; H, 4.97; N, 9.45. Calc for $C_{21}H_{22}BrN_3O_3$: C, 56.77; H, 4.99; N, 9.46). ν_{max}/cm^{-1} 3423, 3324, 3033, 2965, 1719 (C═O), 1577, 1465. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34 (d, J = 8.3 Hz, 2H); 7.25 (m, 5H); 7.07 (d, J = 8.3 Hz, 2H); 5.41 (d, J = 9.3 Hz, 1H); 5.02 (d, J = 8.4 Hz, 2H); 4.89 (m, 1H); 3.91 (s, 2H); 2.12 (m, 1H); 0.83 (d, J = 6.8 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.8; 168.7; 155.8; 135.8; 134.1; 131.7; 130.5; 128.5; 128.2; 128.1; 121.1; 67.2; 54.0; 32.5; 31.5; 18.5; 17.7. MS m/z 444 (M+H).

(*S*)-benzyl-1 (3-(4-bromobenzyl)-1,2,4-oxadiazol-5-yl)benzylcarbamate 5(XVIII)

Yield (0.34, 69%). Pale orange oil. $[\alpha]_D^{20}$ −9.7 (c 2.14 in DCM). R_f 0.23 (hexane/EtOAc: 70/30). (Found: C, 60.93; H, 4.48; N, 8.50. Calc for $C_{25}H_{22}BrN_3O_3$: C, 60.98; H, 4.50; N, 8.53). ν_{max}/cm^{-1} 3543, 3342 2987, 2956, 1732 (C═O), 1565, 1545, 1463. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (d, J = 8.3 Hz, 2H); 7.31 (m, 5H); 7.19 (m, 3H); 7.08 (d, J = 8.3 Hz, 2H); 6.93 (m, 2H); 5.45 (m, 1H); 5.37 (m, 1H); 5.07 (s, 2H); 3.95 (s, 2H); 3.19 (d, J = 4.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.4; 168.7; 155.3; 135.8; 134.5; 134.1; 131.7; 130.5; 129.1; 129.0; 128.6; 128.2; 128.0; 127.3; 121.0; 67.2; 49.7; 39.6; 31.4. MS m/z 492 (M+H).

(*S*)-*tert*-butyl 1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)ethylcarbamate 5(XIX)

Yield (0.24 g, 72%). Pale yellow oil. $[\alpha]_D^{20}$ −34.2 (c 1.08 in DCM). R_f 0.29 (hexane/EtOAc: 90/10). (Found: C, 61.27; H, 6.93; N, 12.58. Calc for $C_{17}H_{23}N_3O_4$: C, 61.25; H 6.95; N, 12.60). ν_{max}/cm^{-1} 3434, 3344, 3054, 2982, 2934, 2838, 1715 (C═O), 1513, 1455. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.22 (d, J = 8.5 Hz, 2H); 6.82 (d, J = 8.6 Hz, 2H); 5.24 (s, 1H); 5.03 (m, 1H); 3.97 (s, 2H); 3.74 (s, 3H); 1.51 (d, J = 7.1 3H); 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 180.0; 169.5; 158.6; 129.9; 127.2; 114.0; 112.3; 60.3; 55.1; 31.3; 28.1; 19.8; 14.1. MS m/z 334 (M+H).

(*S*)-*tert*-butyl 1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-phenylcarbamate 5(XX)

Yield (0.33 g, 83%). Pale yellow oil. R_f 0.57 (hexane/EtOAc: 80/20). (Found: C, 66.85; H, 6.39; N, 10.66. Calc for $C_{22}H_{25}N_3O_4$: C, 66.82; H 6.37; N, 10.63). ν_{max}/cm^{-1} 3033, 2977, 2932, 1716 (C═O), 1612, 1578, 1513. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34 (s, 5H); 7.22 (d, J = 8.4 Hz, 2H); 6.84 (d, J = 8.5 Hz, 2H); 6.09 (s, 1H); 5.65 (s, 1H); 4.01 (s, 2H); 3.78 (s, 3H); 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.5; 169.9; 158.9; 130.2; 129.4; 129.1; 128.8; 127.4; 127.3; 114.3; 109.4; 60.6; 55.5; 31.6; 28.4; 14.4. MS m/z 396 (M+H).

(*S*)-*tert*-butyl 1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methylbutylcarbamate 5(XXI)

Yield (0.34 g, 92%). Pale yellow oil. $[\alpha]_D^{20}$ −35.8 (c 1.37 in DCM). R_f 0.53 (hexane/EtOAc: 60/40). ν_{max}/cm^{-1} 3037, 2960, 2934, 2871, 1716 (C═O), 1613, 1513, 1465. (Found: C, 63.97; H, 7.80; N, 11.16. Calc for $C_{20}H_{29}N_3O_4$: C, 63.98; H 7.79; N, 11.19). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.23 (m, 2H); 6.84 (m, 2H); 5.04 (s, 1H); 4.40 (s, 2H); 3.77 (s, 3H); 3.72 (s, 1H); 1.69 (s, 2H); 1.44 (s, 9H); 0.95 (s, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 180.3; 169.8; 158.9; 130.2; 129.3; 127.5; 114.3; 60.6; 55.4; 52.3; 46.9; 31.6; 28.4; 24.8; 22.8. MS m/z 376 (M+H).

(*S*)-benzyl 1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-2-methylpropylcarbamate 5(XXII)

Yield (0.27 g, 70%). Pale yellow oil. $[\alpha]_D^{20}$ −32.2 (c 0.89 in DCM). R_f 0.45 (hexane/EtOAc: 80/20). (Found: C, 66.80; H, 6.34; N, 10.59. Calc for $C_{22}H_{25}N_3O_4$: C, 66.82; H 6.37; N, 10.63). ν_{max}/cm^{-1} 3034, 2965, 2876, 2836, 1717 (C═O), 1612, 1575, 1455. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32 (s, 5H); 7.19 (m, 2H); 6.84 (m, 2H); 5.62 (m, 1H); 5.01 (s, 2H); 4.96 (m, 1H); 3.98 (s, 2H); 3.75 (s, 3H); 2.19 (m, 1H); 0.91 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.5; 169.4; 158.5; 155.8; 135.9; 129.8; 128.4; 128.1; 128.0; 127.1; 112.9; 67.1; 55.1; 53.9; 32.5; 31.2; 18.4; 17.6. MS m/z 396 (M+H).

(*S*)-benzyl 2-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)pyrrolidine-1-carboxylate 5(XXIII)

Yield (0.29 g, 76%). Pale yellow oil. $[\alpha]_D^{20}$ −69.8 (c 0.45 in DCM). R_f 0.36 (hexane/EtOAc: 60/40). (Found: C, 67.13; H, 5.87; N, 10.71. Calc for $C_{22}H_{23}N_3O_4$: C, 67.16; H 5.89; N, 10.68). ν_{max}/cm^{-1} 3063, 3033, 2956, 1705 (C═O), 1583, 1513, 1455.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.18 (m, 7H); 6.78 (m, 2 H); 5.06 (m, 3H); 3.91 (m, 2H); 3.66 (m, 3H); 3.4 8(m, 2H); 2.21 (m, 2H); 1.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.5; 169.4; 158.9; 158.3; 135.8; 129.6; 129.5; 128.7; 128.1; 128.0; 113.7; 59.9; 54.9; 54.8; 46.5; 31.9;31.0; 20.6. MS m/z 394 (M+H).

5-benzyl-3-(4-methoxybenzyl)-1,2,4-oxadiazole 5(XXIV)

Yield (0.23 g, 84%). Pale yiellow oil. R_f 0.38 (hexane/EtOAc: 90/10). (Found: C, 72.81; H, 5.73; N, 9.96. Calc for $C_{17}H_{16}N_2O_2$: C, 72.84; H 5.75; N, 9.99). ν_{max}/cm^{-1} 3054, 3004, 2958, 2936, 1612, 1577, 1513. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29 (m, 5H);

7.23 (d, J = 8.7 Hz, 2H); 6.52 (d, J = 8.5 Hz, 2H); 4.16 (s, 2H); 3.98 (s, 2H); 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 177.9; 169.8; 158.6; 133.4; 129.9; 129.0; 128.8; 127.5; 127.3; 114.0; 55.1; 32.9; 31.4. MS m/z 281 (M+H).

5-phenyl-3-(4-methoxybenzyl)-1,2,4-oxadiazole 5(XXV)

Yield (0.24 g, 90%). Pale yellow solid. mp 86–88 °C. R_f 0.41 (hexane/EtOAc: 90/10). (Found: C, 72.18; H, 5.28; N, 10.50. Calc for $C_{16}H_{14}N_2O_2$: C, 72.16; H 5.30; N, 10.52). ν_{max}/cm^{-1} 3071, 3034, 3008, 2965, 2928, 2832, 1609, 1560, 1510, 1477. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (d, J = 6.8 Hz, 2H); 7.50 (m, 3H); 7.30 (d, J = 8.6 Hz, 2H); 6.87 (d, J = 8.7 Hz, 2H); 4.08 (s, 2H); 3.77 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.9; 170.6; 158.9; 132.8; 130.3; 129.2; 128.3; 127.8; 124.5; 114.4; 55.5; 31.8. MS m/z 267 (M+H).

5-(3-methylbenzyl)-3-(methylthiomethyl)-1,2,4-oxadiazole 5(XXVI)

Yield (0.14 g, 58%). Pale yellow oil. R_f 0.51 (hexane/EtOAc: 90/10). (Found: C, 61.49; H, 5.59; N, 11.54. Calc for $C_{12}H_{14}N_2OS$: C, 61.51; H 6.02; N, 11.96). ν_{max}/cm^{-1} 3024, 2918, 2863, 1576, 1424, 1362. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.17 (m, 4H); 4.18 (s, 2H); 3.68 (s, 2H); 2.34 (s, 3H); 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.49; 168.14; 138.61; 133.1; 129.6; 128.7; 128.3; 125.9; 32.88; 27.9; 21.3; 15.6. MS m/z 235 (M+H).

5-(benzyl)-3-(methylthiomethyl)-1,2,4-oxadiazole 5(XXVII)

Yield (0.14 g, 62%). Pale yellow oil. R_f 0.37 (hexane/EtOAc: 90/10). (Found: C, 59.99; H, 5.48; N, 12.73. Calc for $C_{11}H_{12}N_2OS$: C, 59.97; H 5.49; N, 12.72). ν_{max}/cm^{-1} 3051, 2982, 2919, 1576, 1496. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33 (m, 5H); 4.23 (s, 2H); 3.68 (s, 2H); 2.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178.4; 168.2; 133.2; 128.9; 128.8; 127.6; 33.0; 27.9; 15.6. MS m/z 221 (M+H).

5-(ethyl-phenylyl)-3-(methylthiomethyl)-1,2,4-oxadiazole 5(XXVIII)

Yield (0.16 g, 67%). Pale yellow oil. R_f 0.53 (hexane/EtOAc: 90/10). (Found: C, 61.49; H 5.98; N, 11.95. Calc for $C_{12}H_{14}N_2OS$: C, 61.51; H 6.02; N, 11.96). ν_{max}/cm^{-1} 3084, 3061, 3025, 2918, 2859, 1578, 1496, 1453, 1362. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.23 (m, 5H); 3.69 (s, 2H); 2.89 (t, J = 7.6 Hz, 2H); 2.73 (t, J = 7.6 Hz, 2H); 2.15 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 180.1; 168.0; 140.5; 128.5; 128.4; 126.2; 34.9; 27.9; 25.9; 15.6. MS m/z: 235 (M+H).

***tert*-butyl (1*S*)-2-methyl-1-(3-(methylthiomethyl)-1,2,4-oxadiazol-5-yl)butylcarbamate 5(XXIX)**

Yield (0.22 g, 71%). Yellow oil. $[\alpha]_D^{20}$ –25.0 (c 0.22 in DCM). R_f 0.80 (hexane/EtOAc: 80/20). (Found: C, 53.29; H 7.98; N, 13.29. Calc for $C_{14}H_{25}N_3O_3S$: C, 53.31; H 7.99; N, 13.32). ν_{max}/cm^{-1} 3061, 2968, 2933, 2878, 1718 (C═O), 1576, 1508, 157, 1367. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.23 (d, J = 8.9 Hz, 1H); 4.98 (m, 1H); 3.69 (s, 2H); 2.11 (s, 3H); 1.96 (m, 1H); 1.43 (s, 9H); 1.20 (m, 2H); 1.00(m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.7; 168.1; 155.5; 52.9; 52.1; 39.4; 28.5; 28.1; 25.3; 15.7; 15.4; 11.6. MS m/z 316 (M+H).

(*S*)-*tert*-butyl 1-(3-(methylthiomethyl)-1,2,4-oxadiazol-5-yl)-2-phenylethylcarbamate 5(XXX)

Yield (0.25 g, 74%). Pale yellow oil. $[\alpha]_D^{20}$ –9.26 (c 0.46 in DCM). R_f 0.71(hexane/EtOAc: 80/20). (Found: C, 58.41; H 6.60; N, 11.99. Calc for $C_{17}H_{23}N_3O_3S$: C, 58.43; H 6.63; N, 12.02). ν_{max}/cm^{-1} 3063, 3029, 2977, 2921, 1716 (C═O), 1575, 1506, 1455, 1367. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.25 (m, 3H); 7.04 (m, 2H); 5.32 (m, 1H); 5.16 (d, J = 8.5 Hz, 1H); 3.68 (s, 2H); 3.24 (m, 2H); 2.09 (s, 3H); 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.1; 167.9; 134.9; 129.2; 128.7; 127.3; 49.3; 44.3; 39.9; 28.2; 27.8; 15.4. MS m/z 350 (M+H).

(*S*)-*tert*-butyl 1-(3-((*R*)-*tert*-butyl ethylcarbamate)-1,2,4-oxadiazol-5-yl)ethylcarbamate 5(XXXI)

Yield (0.25 g, 65%). Pale yellow oil. $[\alpha]_D^{20}$ –59.2 (c 0.78 in DCM). R_f 0.55 (hexane/EtOAc: 70/30). (Found: C, 58.44; H, 6.68; N, 14.33. Calc for $C_{19}H_{26}N_4O_5$: C, 58.45; H, 6.71; N, 14.35). ν_{max}/cm^{-1} 3955, 2981, 1718 (C═O), 1506, 1456. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.25 (s, 5H); 5.60 (d, J = 7.9 Hz, 1H); 5.33 (d, J = 8.1 Hz, 1H); 5.02 (m, 4H); 1.44 (m, 6H); 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 178180.5; 171.1; 155.3; 154.6; 136.1; 128.4; 128.0; 109.1; 80.3; 66.9; 60.2; 43.9; 29.5; 28.1; 20.2. MS m/z 391 (M+H).

Preparation of (*S*)-1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methylbutan-1-amine 6

Trifluoro acetic acid (0.63 mL, 8.2 mmol) was added to a solution of **5(XXI)** (0.31 g, 0.82 mmol) in DCM (10 mL) at room temperature. After 2.5 h the TLC analysis showed the complete absence of the starting material and the reaction mixture was extracted with 5% HCl aqueous solution. The HCl aqueous solution was then added with a saturated solution of $NaHCO_3$ until pH 8 at 0 °C. The aqueous solution was extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to give the (*S*)-1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methylbutan-1-amine **6** in good yield (0.26 g, 95%) as a pale yellow oil. $[\alpha]_D^{20}$ –7.50 (c 0.88 in DCM). R_f 0.66 (hexane/EtOAc: 60/40). (Found: C, 65.41; H, 7.65; N, 15.29. Calc for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26). ν_{max}/cm^{-1} 3379, 3368, 3036, 3001, 2958, 28702837, 1613, 1574, 1513, 1465. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.21 (m, 2H); 6.86 (m, 2H); 4.14 (m, 1H); 3.98 (s, 2H); 3.76 (m, 3H); 1.67 (m, 3H); 0.92 (t, J = 6.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 183.3; 169.7; 158.8; 130.2; 129.2; 127.6; 122.0; 60.5; 55.3; 47.6; 31.6; 24.8; 22.0. MS m/z 276 (M+H).

Preparation of (*S*)-1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methyl-*N*-((*R*)-2,2,2(trifluoro-1-methoxy-1-phenylethyl) butan-1-amine 7

A sample of compound **6** (0.9 g, 0.34 mmol) and (*S*)-(+)-a-methoxy-a-trifluoromethylphenylacetyl chloride (MPTACl) (73 µL,0.39 mmol) were mixed with dry pyridine (0.28 mL) and DCM (0.28 mL) and allowed to stand for 6 h. The mixture of reaction was added with water and extracted

three times with Et_2O. The organic phase was washed with a saturated solution of Na_2CO_3, H_2O and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residual crude (*S*)-1-(3-(4-methoxybenzyl)-1,2,4-oxadiazol-5-yl)-3-methyl-*N*-((*R*)-2,2,2(trifluoro-1-methoxy-1-phenylethyl) butan-1-amine **7** in good yield (0.47 g, 96%) was characterized. $[\alpha]_D^{20}$ –34.9315 (*c* 0.0032 in DCM). R_f 0.53 (hexane/EtOAc: 60/40). (Found: C, 61.05; H, 5.72; N, 8.56. Calc for $C_{25}H_{28}F_3N_3O_4$: C, 61.09; H, 5.74; N, 8.55). ν_{max}/cm^{-1} 3054, 2921, 2872, 1694(C═O), 1662, 1578, 1513, 1465. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40 (m, 5H); 7.21 (d, J = 8.8 Hz, 2H); 6.85 (d, J = 8.8 Hz, 2H); 5.41 (q, J = 8.7 Hz, 1H); 4.00 (s, 2H); 3.79 (s, 3H); 3.28 (s, 3H); 1.83 (t, J = 7.0 Hz, 2H); 1.67 (m, 1H); 0.97 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 179.0; 169.6; 158.6; 150.9; 131.4; 129.9; 129.5; 129.0; 128.5; 127.9; 127.1; 114.0; 109.1; 55.2; 54.8; 45.2; 42.2; 33.4; 24.6; 22.6; 21.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm): –70.387. MS m/z 492 (M+H).

Acknowledgements

This work was financially supported by Regione Autonoma della Sardegna ("Sintesi e caratterizzazione delle proprietà chimiche e degli effetti neuromodulatori sul SNC di una libreria di donatori di nitrossido derivati dell'acido di Piloty")

Notes and references

1 J. C. Jochims, In *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees and E. V. F. Scriven, ed.; Pergamon Press: London, 1996; chapter 4; and references therein.

2 (*a*) G. D. Diana, D. L. Volkots, T. J. Nitz, T. R. Bailey, M. A. Long, N. Vescio, S. Aldous, D. C. Pevear and F. J. Dutko, *J. Med. Chem.*, 1994, **37**, 2421; (*b*) K. E. Andersen, B. F. Lundt, A. S. Joergensen and C. Braestrup, *Eur. J. Med. Chem.*, 1996, **31**, 417.

3 S. Borgs, G. Estenne-Bouhtou, K. Luthman, I. Csoregh, W. Hesselink and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 3112.

4 S. Borg, R. C. Vollinga, M. Labarre, K. Payza, L. Terenius and K. Luthman, *J. Med. Chem.*, 1999, **42**, 4331.

5 (*a*) J. L. Buchanan, C. B. Vu, T. J. Merry, E. G. Corpuz, S. G. Pradeepen, U. N. Mani, M. Yang, H. R. Plake, V. M. Varkhedkar, B. A. Lynch, I. A. MacNeil, K. A. Loiacono, C. L. Tiong and D. A. Holt, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2359; (*b*) C. B. Vu, E. G. Corpuz, T. J. Merry, S. G. Pradeepan, C. Barlett, R. S. Bohacek, M. C. Botfield, C. J. Eyermann, B. A. Lynch, I. A. MacNeil, M. K. Ram, M. R. van Schravendijk, S. Violette and T. K. Sawyer, *J. Med. Chem.*, 1999, **42**, 4088.

6 P. L. Durette, W. K. Hagmann, I. E. Kopka, M. MacCossMerck & Co., WO 00/71572 A1, 30 Nov. 2000.

7 L. J. Street, R. Baker, T. Book, C. O. Kneen, A. M. MacLeod, K. J. Merchant, G. A. Showell, J. Saunders, R. H. Herbert, S. B. Freedman and E. A. Harley, *J. Med. Chem.*, 1990, **33**, 2690.

8 G. D. Diana, D. L. Volkots, T. J. Nitz, T. R. Bailey, M. A. Long, N. Vescio, S. Aldous, D. C. Pevear and F. J. Dotko, *J. Med. Chem.*, 1994, **37**, 2421.

9 J. Roppe, N. D. Smith, D. Huang, L. Tehrani, B. Wang, J. Anderson, J. Brodkin, J. Chung, X. Jiang, C. King, B. Munoz, M. A. Varney, P. Prasit and N. D. P. Cosford, *J. Med. Chem.*, 2004, **47**, 4645.

10 C. J. Swain, R. Baker, C. Kneen, J. Moseley, J. Saunders, E. M. Seward, G. Stevenson, M. Beer, J. Stanton and K. Watling, *J. Med. Chem.*, 1991, **34**, 140.

11 (*a*) Z. Li, W. Chen, J. J. Hale, C. L. Lynch, S. G. Mills, R. Hajdu, C. A. Keohane, M. J. Rosenbach, J. A. Milligan, G.-J. Shei, G. Chrebet, S. A. Parent, J. Bergstrom, D. Card, M. Forrest, E. J. Quackenbush, L. A. Wickham, H. Vargas, R. M. Evans, H. Rosen and S. Mandala, *J. Med. Chem.*, 2005, **48**, 6169; (*b*) J. P. Heer, T. D. Heightman and J. Skidmore, E.P. Patent 067971, 2009; (*c*) J. P. Heer and T. D. Heightman, E.P. Patent 067963, 2009; (*d*) E. Roberts, H. Rosen, S. Brown, M. Morales, X. Peng and R. Poddutoori, U.S. Patent 003014, 2009; (*e*) A. J. Dyckman, W. J. Pitts and S. H. Watterson, U.S. Patent 021696, 2010.

12 (*a*) S. Borg, G. Estenne-Bouhtou, K. Luthman, I. Csoregh, W. Hesselink and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 3112; (*b*) T. L. Deegan, T. J. Nitz, D. Cebzanoz, D. E. Pufko and J. A. Porco, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 209; (*c*) J. L. Buchanan, C. B. Vu, T. J. Merry, M. E. G. Corpuz, S. G. Pradeepan, U. N. Mani, M. Yang, H. R. Plake, V. M. Varkhedkar, B. A. Lynch, I. A. MacNeil, K. A. Loiacono, C. L. Tiong and D. A. Holt, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2359; (*d*) K. Rice and J. M. Nuss, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 753; (*e*) A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang and K. D. Rice, *Tetrahedron Lett.*, 2001, **42**, 1441; (*f*) A. Hamzé, J-F. Hernandez, P. Fulcrand and J. Martimnez, *J. Org. Chem.*, 2003, **68**, 7316 and references therein.

13 A. R. Katritzky, A. A. Shestopalov and K. Suzuki, *ARKIVOC*, 2005, **7**, 36.

14 (*a*) Y Wang, R. L. Miller, D. R. Sauer and S. W. Djuric, *Org. Lett.*, 2005, **7**, 925; (*b*) M. Adib, M. Mahadavi, N. Mahmoodi, H. Pirelahi and H. R. Bijanzadeh, *Synlett*, 2006, 1765; (*c*) M. Adib, A. H. Jahromi, N. Tavoosi, M. Mahadavi and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2965; (*d*) K. K. D. Amarasinghe, M. B. Maier, A. Srivastava and J. L. Gray, *Tetrahedron Lett.*, 2006, **47**, 3629.

15 L. De Luca and G. Giacomelli, *J. Org. Chem.*, 2008, **73**, 3967 and references therein.

16 All microwave reactions were performed on a CEM Discover Synthesis Unit in sealed vessels.

17 (*a*) C. O. Kappe and D. Dallinger, *Mol. Diversity*, 2009, **13**, 71; (*b*) C. O. Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127; (*c*) C. O. Kappe and D. Dallinger, *Nat. Rev. Cancer*, 2005, **5**, 51.

18 (*a*) C. La Motta, S. Sartini, S. Salerno, F. Simorini, S. Taliani, A. M. Marini, F. Da Settimo, L. Marinelli, V. Limongelli and E. Novellino, *J. Med. Chem.*, 2008, **51**, 3182; (*b*) G. P. Moloney, J. A. Angus, A. D. Robertson, M. J. Stoermer, M. Robinson, C. E. Wright, K. McRae and A. Christopoulos, *Eur. J. Med. Chem.*, 2008, **43**, 513.

