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Versatile strategies for the solid phase synthesis of small heterocyclic scaffolds: [1,3,4]-thiadiazoles and [1,3,4]-oxadiazoles

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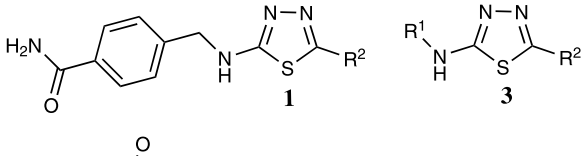
Abstract—New robust protocols for the solid phase synthesis of 5-alkylthio-, 5-alkyl/aryl-, and 5-acylamino-2-alkylamino-[1,3,4]-thiadiazoles are described based on a common resin bound thiosemicarbazide. A protocol for the solid phase synthesis of 2-alkyl/aryl-amino-5-alkylamino-[1,3,4]-oxadiazoles from a resin bound semicarbazide is likewise reported. The protocols have been verified by the preparation of four small libraries that all gave products in good to excellent yields and purity.

1. Introduction

Parallel synthesis has over the last 20 years evolved into a well established and essential medicinal chemist's tool for the rapid preparation of screening libraries as well as accelerating the lead optimization process.[1] Initially screening libraries were designed with focus on diversity and number of compounds,[2] but later Lipinski invited awareness towards the importance of their 'drug-like' physiochemical properties.[3] More recently the concept of 'lead-like' was introduced by Teague et al.[4,5] They investigated a number of drugs and their corresponding leads and found that size and lipophilicity in general increases through the lead-optimization process. Based on these findings they suggest that screening libraries should consist of lead-like compounds with physiochemical properties in the range $M_w < 350$ and $1 < c \log P < 3$.



In recent publications we have described several novel solid phase synthesis strategies for the preparation of [1,3,4]-thiadiazoles[6] **1** and [1,3,4]-oxadiazoles[7] **2**. However, the reported strategies proceeded with the aid of a relatively large 'spacer' and thus the products were inapplicable in the context of lead-like criteria and investigations were thus directed towards reducing the generic scaffold size. In this communication we would like to present both new and revised solid phase synthesis strategies for the formation of substituted [1,3,4]-thiadiazoles **3** and [1,3,4]-oxadiazoles **4**.

2. Results and discussion

An obvious attachment point to a solid support for thiadiazole **3** and oxadiazole **4** is the secondary heteroarylamine. One possible approach for such an attachment is to use a backbone amide linker (BAL)[8] either as a di- or a trialkoxybenzyl amine. In general the resin bound tertiary amines formed when employing such resins do not undergo acidolytic cleavage. However, a few examples are known where substituted anilines[9] or aminothiazoles[10] have been released under acidic conditions. Due to the heteroaromatic character of the thiadiazole- and oxadiazole amines we expected that these would undergo acidolytic cleavage.

Hence, the commercially available 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene[11] was treated with a range of primary amines under standard reductive amination conditions to yield the respective resin bound benzyl amine derivates **5** as depicted in Scheme 1. In our previous paper we reported the transformation of a resin bound primary amine to an isothiocyanate upon treatment with di-(2-pyridyl)-thionocarbonate (DPT).[6] The

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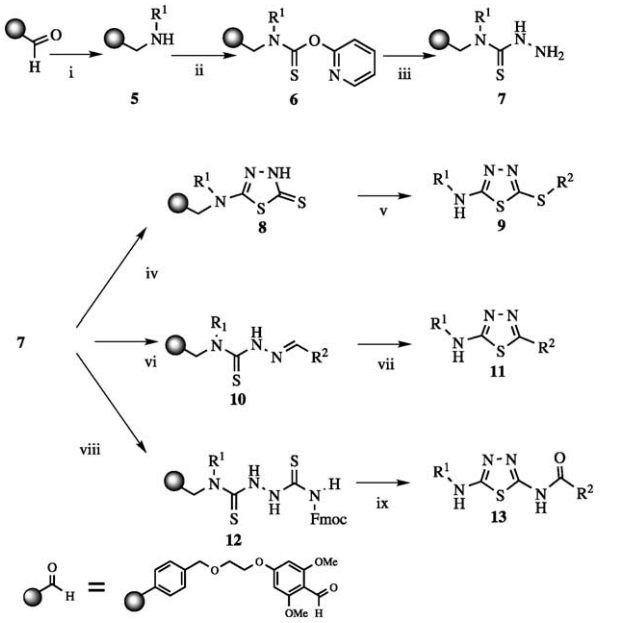


Scheme 1. Reagents and condition. (i) (a) R^1NH_2, 5% AcOH, NMP/MeOH, 1 h; (b) $NaBH_3CN$, NMP/MeOH, 12 h; (ii) DPT, NMP, 50 °C, 16 h; (iii) $H_2NNH_2 \cdot H_2O$, DMSO, 50 °C 14 h; (iv) DPT, DCM, 3 h; (v) (a) 1,4-dioxane/MeOH/$NaOH_{aq}$ (1 N), 30 min; (b) R^2Br, 1,4-dioxane, 14 h; (c) TFA/DCM, 2 h (vi) R^2CHO, TMOF/NMP, (2+14) h; (vii) (a) $FeCl_3$, DCM/MeOH, (2+14) h; (b) TFA/DCM, 2 h; (viii) FmocNCS, DCM, DIPEA, 14 h; (ix) (a) EDC, NMP, 50 °C, 14 h; (b) DMF/piperidine (2+20) min; (c) R^2COOH, DIIC, DMAP, DIPEA, NMP/DCM; (d) TFA/DCM, 2 h.

isothiocyanate was subsequently reacted with hydrazine to give a thiosemicarbazide.

In this approach, where the immobilized secondary amine has to be converted to the thiosemicarbazide **7**, the intermediate can not be an isothiocyanate. It has been reported that secondary amines react with DPT to give the corresponding 2-pyridyl thiocarbamates.[12] However, the conversion of this to a thiosemicarbazide by treatment with a hydrazine has to our knowledge not been reported and therefore reaction conditions for this transformation had to be developed.

The immobilized amines **5** were treated with DPT under a range of conditions to investigate the formation of the reactive species **6**. A small amount of resin **6** was cleaved with TFA/DCM (50:50) but due to lack of stability of the intermediate released from resin **6** under the cleavage conditions the reaction could not be monitored directly. Instead the reaction was investigated by treatment of resin **6** with hydrazine hydrate and monitoring the formation of thiosemicarbazide **7** by cleavage of a small amount of the resin with TFA/DCM (50:50). LC–MS analysis was performed on the crude residue. When applying the conditions we previously developed for conversion of a resin bound primary amine to a thiosemicarbazide only minimal conversion was observed. Replacing the solvent with 1,3-dichloropropane (DCP) and heating to 50 °C did not improve the result. However, when the reaction was performed in *N*-methyl-2-pyrrolidinone (NMP) for 16 h, almost complete conversion was suggested as interpreted by a negative chloranil test result. The resin bound benzyl-

Table 1. Conditions used to convert resin bound benzyl amine **5a** into benzyl-thiocarbamic acid *O*-pyridin-2-yl ester **6a**

Reagents and conditions	% Purity **7a**		
	20 °C	50 °C	80 °C
5 equiv DPT in DCM	20	—	—
5 equiv DPT in DCP	0	20	—
5 equiv DPT in DMSO	16	57	10
5 equiv DPT in NMP	15	85	73
10 equiv DPT in NMP	22	95	71

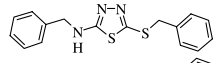
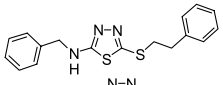
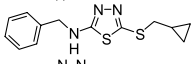
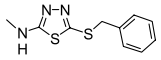
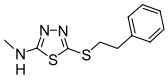
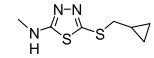
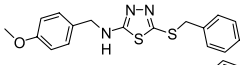
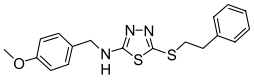
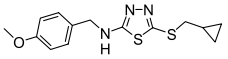
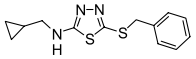
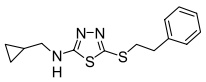
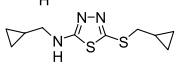
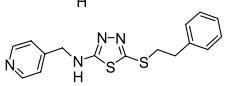
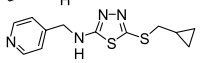
All reactions were run for 12 h. Results are given as percentage purity of the corresponding formation of **7a** (LC–MS, UV peak integration at 214 nm).

thiocarbamic acid *O*-pyridin-2-yl ester **6** was subsequently substituted by treatment with hydrazine in DMSO at 50 °C to form the pivotal thiosemicarbazide **7**. The results are given in Table 1.

Thiosemicarbazide **7** is a versatile intermediate and several derivatisations leading to heterocyclic systems could be imagined from this intermediate. As depicted in Scheme 1 we have investigated three different transformations of thiosemicarbazide **7** to substituted [1,3,4]-thiadiazoles.

Resin bound thiosemicarbazide **7** was treated with 10 equiv DPT in DCM to give immobilized thione **8**.[6] Alkylation of

Table 2. Representative results and structures from the library of 2-alkylthio-5-alkylamino-[1,3,4]-thiadiazoles (**9**)

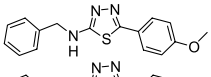
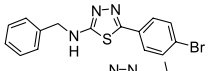
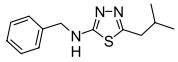
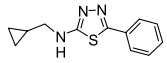
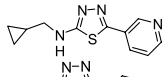
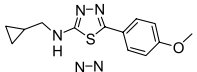
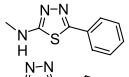
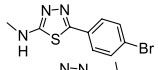
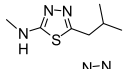
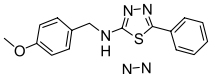
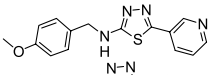
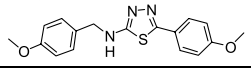
		Purity (%)	Yield (%)
9a[13]		70	65
9b		70	60
9c		70	56
9d[14]		95	72
9e		95	50
9f		90	81
9g		90	71
9h		95	82
9i		90	78
9j		90	73
9k		90	72
9l		60	45
9m		90	64
9n		90	58

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

thione **8** with primary alkyl- or benzyl bromides in 1,4-dioxane yielded a mixture *N*- and *S*-alkylated products. Applying DIPEA in the alkylation procedure did not improve the selectivity for S-alkylation. However, when the resin was treated with a mixture of 1,4-dioxane, methanol and aqueous sodium hydroxide prior to alkylation, only S-alkylation was observed. Employing this procedure thione **8** was treated with a range of alkylating agents to give the corresponding monoalkylated products. Subsequent cleavage with TFA/DCM yielded [1,3,4]-thiadiazoles **9**. The results are given in Table 2.

Intermediate resin bound thiosemicarbazide **7**, was an ideal starting point for the synthesis of substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines **11**. The formation of imine **10** by reaction with aldehydes was therefore investigated. Treatment with aldehydes in a mixture of trimethyl orthoformate (TMOF), NMP and acetic acid (5:5:1) yielded a mixture of products. When applying the same conditions in the absence of acid, the intermediate resin bound thiosemicarbazone **10** was formed. Cyclization of **10** was achieved by treating the resin with a solution of iron(III) chloride in DCM/MeOH.[6] Subsequent cleavage with TFA/DCM yielded substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines **11**. The results are given in Table 3.

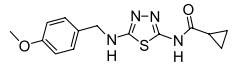
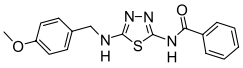
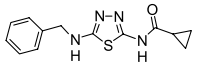
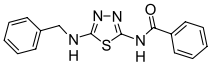
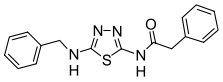
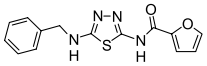
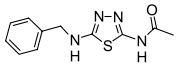
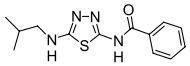
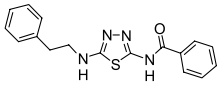
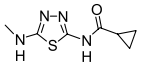
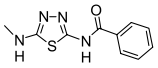
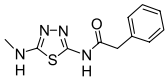
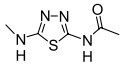
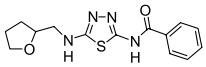
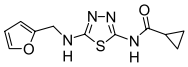
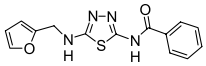
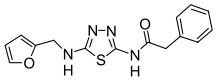
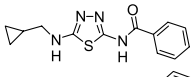
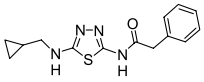
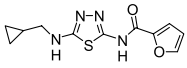
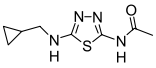
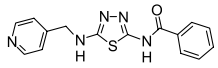
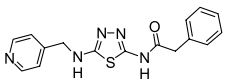
Table 3. Representative results and structures from the library of substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines (**11**)

		Purity (%)	Yield (%)
11a		95	73
11b		91	69
11c[15]		86	72
11d		98	61
11e		81	65
11f		65	47
11g		92	70
11h		98	71
11i		99	76
11j		99	73
11k		98	66
11l		95	61

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

The chemistry discussed above yields substituted 5-thio-1,3,4-thiadiazoles **9** and substituted 5-alkyl-1,3,4-thiadiazoles **11**. As a continuation of this work we sought to synthesize substituted 5-carboxamide-1,3,4-thiadiazoles **13**. To our knowledge, a solid phase synthesis of this scaffold

Table 4. Representative results and structures from the library of *N*-(5-alkylamino-[1,3,4]thiadiazol-2-yl)-amide (**13**)

		Purity (%)	Yield (%)
13a		95	63
13b		91	73
13c		82	59
13d[16]		78	65
13e[16]		90	71
13f		90	80
13g		89	64
13h		85	60
13i		87	86
13j		90	74
13k		94	75
13l		90	71
13m		70	71
13n		90	49
13o		67	51
13p		72	43
13q		59	48
13r		96	72
13s		95	66
13t		61	31
13u		70	59
13v		90	66
13x		95	85

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

has never been reported. Treatment of thiosemicarbazide **7** with a mixture of fmoc-isothiocyanate and DIPEA in DCM yielded resin bound hydrazine-1,2-dicarbothioamide **12**. A range of different conditions were applied in an attempt to cyclizise intermediate **12** as shown in Table 5. 1,3-Diisopropyl carbodiimide (DIIC) in dry DMSO or NMP resulted only in partial cyclization. A mixture of triphenylphosphine and hexachloroethane in dry THF gave good conversion, but the reagent generated acidic conditions resulting in partial resin cleavage. Addition of DIPEA to minimize cleavage resulted in incomplete cyclization. However, treating the resin with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) in DMSO at 80 °C gave almost complete conversion and good yield, similarly EDC·HCl in NMP gave complete conversion and good yield at 50 °C. The latter procedure was chosen for cyclization in the library synthesis due to the lower temperature associated with NMP as the solvent. Immobilized 5-fmoc-amino-1,3,4-thiadiazoles were subsequently deprotected with 20% piperidine in NMP. The resulting 5-amino-1,3,4-thiadiazoles were then acylated with different carboxylic acids using DIIC in DCM/NMP. Cleavage with TFA/DCM yielded substituted 5-carboxamide-1,3,4-thiadiazoles **13**. A small library based on this protocol was prepared. The results are given in Table 4.

Encouraged by the results obtained with the [1,3,4]-thiadiazole scaffolds we decided to investigate the possibility of preparing the analogous [1,3,4]-oxadiazole derivative **16** (Scheme 2). Hence, a resin bound amine **5** was treated with triphosgene and DIPEA in DCM, followed by reaction of the formed reactive intermediate with hydrazine hydrate in DMSO to yield semicarbazide intermediate **14**.

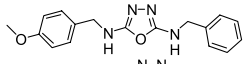
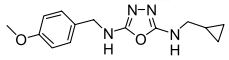
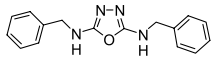
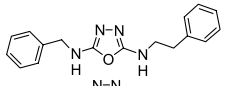
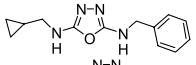
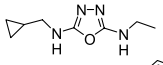
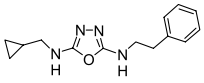
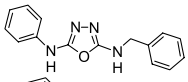
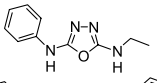
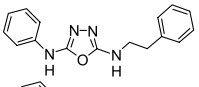
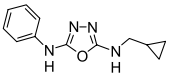
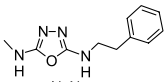
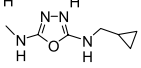
Subsequent addition of various thiocyanates under basic conditions gave the substituted thiobisurea **15**. Again, a range of conditions for the cyclization were investigated. The results are given in Table 5. As for the cyclization of **12**, EDC·HCl in dry NMP were the preferred reaction conditions to convert resin bound **15** into 2,5-diamino-1,3,4-oxadiazole **16**. Cleavage was realized upon treatment with TFA/DCM. The developed protocol was used to generate a small library of substituted 2,5-diamino-1,3,4-oxadiazoles **16**. The results are displayed in Table 6.

Table 5. Selected results for the cyclization of **12** and for the cyclization of **15**

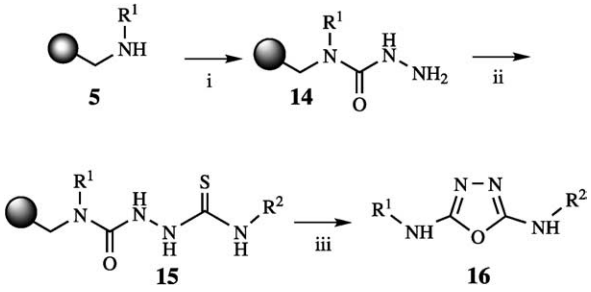
	Reagents and conditions	Cyclization of **12** (%)	Cyclization of **15** (%)
1	DIIC in dry NMP (20 °C)	25	0
2	DIIC in dry NMP (80 °C)	63	33
3	DIIC in dry DMSO (80 °C)	12	5
4	PPh_3 and C_2Cl_6 in THF (20 °C)	95	67
5	PPh_3 and C_2Cl_6 in THF/DIPEA (20 °C)	42	23
6	EDC·HCl in dry DMSO (50 °C)	71	54
7	EDC·HCl in dry DMSO (80 °C)	96	89
8	EDC·HCl in dry NMP (50 °C)	99	97

Results are given as percentage purity of product determined by using LC–MS of the crude cleavage product (UV peak integration at 214 nm). All reactions were run over 14 h.

Table 6. Representative results and structures from library of *N*,*N*-dialkyl-[1,3,4]oxadiazoles-2,5-diamine (**16**)

		Purity (%)	Yield (%)
16a		95	81
16b		95	76
16c		90	73
16d		95	83
16e		83	73
16f		75	58
16g		90	60
16h[17]		95	85
16i[17]		95	87
16j		95	81
16k		95	89
16l		95	72
16m		95	65

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.



Scheme 2. Reagent and conditions. (i) (a) $CO(OCCl_3)_2$, DIPEA, DCM, 5 h; (b) $H_2NNH_2 \cdot H_2O$, DMSO, 14 h; (ii) R^2NCS; DCM, DIPEA, 6 h; (iii) (a) EDC·HCl, dry NMP, 50 °C, 14 h, (b) TFA/DCM, 2 h.

3. Conclusion

In conclusion, we have studied and developed four new versatile solid phase synthesis protocols for the preparation of 'lead-like' substituted [1,3,4]-oxadiazoles and [1,3,4]-thiadiazoles. Treating the highly applicable resin bound thiosemicarbazide with a variety of reagents and conditions yielded, after TFA-mediated cleavage, 5-alkylthio-, 5-alkyl, and 5-acylamino-2-alkylamino-[1,3,4]-thiadiazoles in good yield and purity. In another investigation resin

bound semicarbazide was treated with isothiocyanates and the resulting intermediates after cyclodehydration and TFA-mediated cleavage yielded substituted 2,5-dialkyl-amino-[1,3,4]-oxadiazoles in good yield and purity.

4. Experimental

4.1. General

All reactions where performed in standard glassware or Teflon apparatus suitable for solid-phase synthesis. Starting materials were commercially available and used without further purification. 2-(3,5-Dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene, (200–400 mesh, polystyrene-divinylbenzene 1%, 0.45 mmol/g) was purchased from Novabiochem. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) and are relative to TMS as internal standard. Coupling constants are given in Hertz (J values in Hz). The following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet, dd = double of doublets. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model Spectrum one. Electrospray (ES) mass spectra and LC–MS analyses were recorded on a PE Sciex API 3000 instrument with an HP1100 HPLC equipped with binary pump, column compartment, diode array detector, single quadrupole mass spectrometer detector and a C18 column ((Waters Xterra MS C-18X) 3 mm) at 40 °C with a flow of 1.0 mL/min. Two mobile phases (mobile phase A, 100% water, 0.01% TFA; mobile phase B, 100% acetonitrile, 0.01% TFA) were employed to run a gradient condition from 10–100% B in 7.5 min with UV detection at 210 nm and MS scanning range from 100–1000 amu. Injections of 1 μL were used. Unless stated, all reactions were carried out at 20 °C and washing was performed at a ratio of 1 mL solvent per 100 mg resin. Unless stated, reactions were monitored by cleaving small portion of the resin and analyzing the crude cleavage product on LC–MS. Yields were determined by NMR studies using 2,5-dimethyl-furan as internal standard.

4.2. General procedure for reductive amination of 2-(3,5-dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene (5)

Typical procedure. A solution of benzyl amine (480 mg, 4.50 mmol) in NMP/MeOH/AcOH (10 mL, 5:5:1 v/v) was added to 2-(3,5-dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene resin (1.0 g, 0.45 mmol) pre-swollen in NMP. The mixture was agitated for 30 min before a solution of $NaBH_3CN$ (422 mg, 6.75 mmol) in MeOH/NMP (10 mL, 1:1 v/v) was added. The mixture was shaken for a further 18 h. Excess reagents were removed by filtration and the resin was washed with NMP (3×), MeOH/THF (1:1 v/v) (2×) and DCM (3×). The resin was dried in vacuo overnight at 40 °C.

4.3. Formation of thiosemicarbazide (7)

Typical procedure. A solution of DPT (1.04 g, 4.50 mmol) in dry NMP (15 mL) was added to resin **5** (1.0 g, 0.45 mmol) and the mixture was shaken for 12 h at 50 °C. The resin was filtered before washing with DMSO (3×). A solution of hydrazine hydrate (216 mg, 4.50 mmol) in DMSO (15 mL) was added and the resin was then agitated 14 h at 50 °C before excess reagent was removed by filtration. The resin was washed with DMSO (3×), MeOH/THF (1:1 v/v) (2×), and DCM (3×).

4.4. Synthesis of 5-amino-3H-1,3,4-thiadiazole-2-thione (8)

A solution of DPT (97 mg, 0.42 mmol) in DCM (3 mL) was added to a portion of resin **7** (100 mg, 0.042 mmol). The mixture was agitated for 3 h before excess reagent was removed by filtration and washing using NMP (3×) and DCM (3×).

4.5. Formation of 2-alkylthio-5-alkylamino-[1,3,4]-thiadiazole (9) and resin cleavage

Typical procedure. Resin **8** (100 mg, 0.042 mmol) pre-swollen in 1,4-dioxane was treated with a mixture of 1,4-dioxane/MeOH/$NaOH_{(aq)}$(1 N) (2 mL, 7:3:1, v/v) for 30 min, before a solution of benzylbromide (22 mg, 0.126 mmol) in 1,4-dioxane (3 mL) was added. The resin was agitated 14 h, filtered to remove excess reagents and washed with NMP (3×), MeOH/THF (1:1 v/v) (2×) and DCM (3×). The resin was subsequently cleaved with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **9**.

4.5.1. Benzyl-(5-benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9a). White solid, mp 95.2–95.9 °C; ν_{max} (KBr) 703, 1027, 1092, 1207, 1357, 1426, 1452, 1479, 1547, 3029, 3248 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 4.30 (s, 2H, PhCH_2S), 4.40 (d, J = 5.2 Hz, 2H, PhCH_2NH), 7.33 (m, 10H, ArH), 8.29 (t, J = 5.2 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 38.7 (SCH_2), 48.2 (NHCH_2), 127.5, 127.8, 127.9, 128.7, 128.8, 129.4, 137.4, 138.8, 150.0, 169.9 (ArC). HR-MS (Q-TOF-ES) m/z = 314.0780, calcd for $[C_{33}H_{34}N_4OS + H]^+$ 314.0785.

4.5.2. Benzyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9b). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ = 2.92 (t, J = 7.5 Hz, 2H, PhCH_2CH_2S), 3.31 (t, J = 7.5 Hz, 2H, PhCH_2CH_2S), 4.47 (d, J = 4.9 Hz, 2H, PhCH_2-NH), 7.26 (m, 6H, ArH), 7.35 (d, J = 4.3 Hz, 4H, ArH), 8.31 (t, J = 4.9 Hz, 1H, PhCH_2NH). ES-MS m/z 328 MH^+.

4.5.3. Benzyl-(5-cyclopropylmethylsulfanyl-1,3,4] thiadiazol-2-yl)-amine (9c). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ = 0.25 (m, 2H, CH(CH_2CH_2)), 0.51 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH_2CH_2)), 3.02 (d, J = 7.1, 2H, SCH_2cPr), 4.46 (d, J = 5.6 Hz, 2H, PhCH_2NH), 7.29 (m, 1H, ArH), 7.34 (d, J = 4 Hz, 4H, ArH), 8.29 (t, J = 5.6 Hz, 1H, PhCH_2NH). ES-MS m/z 278 MH^+.

4.5.4. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (9d).[14] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.83 (d, J=3.9 Hz, 3H, CH_3NH), 4.30 (s, 2H, SCH_2Ph), 7.32 (m, 5H, ArH), 7.71 (q, J=3.9 Hz, 1H, CH$_3$NH). ES-MS m/z 238 MH$^+$.

4.5.5. Methyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.86 (d, J=4.8 Hz, 2H, CH_3NH), 2.94 (t, J=7.6 Hz, 2H, PhCH_2CH$_2$), 3.31 (t, J=7.6, 2H, PhCH$_2$CH_2), 7.26 (m, 5H, ArH), 7.74 (q, J=4.8 Hz, 1H, CH$_3$NH). ES-MS m/z 252 MH$^+$.

4.5.6. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (9f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.53 (m, 2H, CH(CH_2CH_2)), 1.05 (m, 1H, CH(CH$_2$CH$_2$)), 2.85 (d, J=4.7 Hz, 3H, CH_3NH), 3.01 (d, J=7.0 Hz, SCH_2), 7.71 (q, J=4.7 Hz, 1H, NH). ES-MS m/z 202 MH$^+$.

4.5.7. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-(4-methoxy-benzyl)-amine (9g). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.73 (s, 3H, CH_3O), 4.30 (s, 2H, SCH_2Ph), 4.35 (d, J=5.5 Hz, 2H, CH_2NH), 6.89 (d, J=6.6 Hz, 2H ArH), 7.30 (m, 7H, ArH), 8.21 (t, J=5.5 Hz, NH). ES-MS m/z 344 MH$^+$.

4.5.8. (4-Methoxy-benzyl)-(5-phenethylsulfanyl-1,3,4]thiadiazol-2-yl)-amine (9h). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.94 (t, J=7.6 Hz, 2H, PhCH_2CH$_2$), 3.31 (t, J=7.5 Hz, 2H, PhCH$_2$CH_2), 3.73 (s, 3H, CH_3O), 4.38 (d, J=5.6 Hz, 2H, CH_2NH), 6.91 (d, J=8.6 Hz, 2H, ArH), 7.25 (m, 7H, ArH), 8.23 (t, J=5.6 Hz, 1H, NH). ES-MS m/z 358 MH$^+$.

4.5.9. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-(4-methoxy-benzyl)-amine (9i). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.53 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 2H, SCH_2), 3.73 (s, 3H, CH_3O), 4.37 (d, J=6.4 Hz, CH_2NH), 6.89 (d, J=8.6 Hz, 2H, ArH), 7.27 ((d, J=8.6 Hz, 2H, ArH), 8.21 (t, J=6.4 Hz, 1H NH). ES-MS m/z 307 MH$^+$.

4.5.10. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-cyclopropylmethyl-amine (9j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.20 (m, 2H, CH(CH_2CH_2)), 0.45 (m, 2H, CH(CH_2CH_2)), 1.03 (m, 1H, CH(CH$_2$CH$_2$)), 3.11 (dd, J_1=6.6 Hz, J_2=5.6 Hz, CHCH_2NH), 4.30 (s, 2H, SCH_2), 7.23 (m, 5H, ArH), 7.89 (t, J=5.6 Hz, 1H NH). ES-MS m/z 278 MH$^+$.

4.5.11. Cyclopropylmethyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9k). White solid, mp 66.9–67.2 °C; ν_{max} (KBr) 1045, 1205, 1278, 1327, 1542, 3003, 3232 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.22 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 2.94 (t, J=7.4 Hz, 2H, PhCH_2CH$_2$), 3.13 (dd, J_1=5.5 Hz, J_2=7.1 Hz, 2H, cPrCH_2NH), 3.31 (t, J=7.4 Hz, 2H, PhCH$_2$CH_2), 7.25 (m, 5H, ArH), 7.91 (t, J=5.5 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ=3.3, 10.3, 34.96, 36.40, 50.0, 126.3, 128.3, 128.5, 139.4, 149.4, 169.3. HR-MS (Q-TOF-ES) m/z=292.0937, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 292.0942.

4.5.12. Cyclopropylmethyl-(5-yclopropylmethyl-sulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.25 (m, 4H, CH(CH_2CH_2)), 0.50 (m, 4H, CH(CH_2CH_2)), 1.07 (m, 2H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 2H, SCH_2cPr), 3.12 (dd, J_1=5.5 Hz, J_2=6.6 Hz, 2H, cPrCH_2NH), 7.89 (t, J=5.5 Hz, 1H, NH). ES-MS m/z 242 MH$^+$.

4.5.13. (5-Phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-pyridin-4-ylmethyl-amine (9m). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.94 (t, J=7.3 Hz, 2H, CH$_2$CH_2Ph), 3.33 (t, J=7.3 Hz, 2H, CH_2CH$_2$Ph), 4.58 (d, J=5.8 Hz, 2H, CH_2NH), 7.24 (m, 5H, ArH), 7.46 (d, J=5.5 Hz, 2H, ArH), 8.44 (t, J=5.8 Hz, NH), 8.58 (d, J=6.1 Hz, 2H, ArH). ES-MS m/z 329 MH$^+$.

4.5.14. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-pyridin-4-ylmethyl-amine (9n). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.25 (m, 2H, CH(CH_2CH_2)), 0.55 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 1H, SCH_2cPr), 3.03 (d, J=7.5 Hz, 1H, SCH_2cPr), 4.57 (d, J=5.2, 2H, PyCH_2NH), 7.45 (br s, 2H, ArH), 8.43 (t, J=5.2 Hz, 1H, NH), 8.59 (br s, 2H, ArH). ES-MS m/z 279 MH$^+$.

4.6. Formation of substituted thiosemicarbazide (10)

General procedure. A solution of 4-methoxybenzaldehyde (57 mg, 0.42 mmol) in TMOF/NMP (1:1, v/v, 3 mL) was added to resin **7** (100 mg, 0.042 mmol) and the resulting mixture agitated for 2 h. Excess reagents were removed by filtration before a new portion of aldehyde was added to the resin and the mixture was agitated for 14 h. Excess reagents were removed by filtration and the resin was washed with NMP (3×), THF/MeOH (1:1 v/v) (2×) and DCM (3×).

4.7. Formation of 5-alkyl-[1,3,4]thiadiazol-2-yl) alkyl amine (11)

General procedure. $FeCl_3$ (34 mg, 0.21 mmol) dissolved in DCM/MeOH (2 mL, 2:1 v/v) was added to resin **10** and agitated for 2 h. Excess reagents were removed by filtration and the, a new protion of $FeCl_3$ was added and the mixture aggitated for 14 h. The resin was filtered and washed with DCM (2×), NMP (2×), MeOH/DCM (1:1 v/v) (2×) and DCM (5×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding title products **11**.

4.7.1. Benzyl-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11a). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.30 (s, 3H, OCH_3), 4.52 (d, J=5.8 Hz, 2H, NHCH_2), 7.02 (d, J=9.1 Hz, 2H, ArH), 7.28 (m, 1H, ArH), 7.37 (m, 4H, ArH), 7.67 (d, J=9.1 Hz, 2H, ArH), 8.35 (t, J=5.8 Hz, 1H, NHCH$_2$). ES-MS m/z 298 MH$^+$.

4.7.2. Benzyl-[5-(4-bromo-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11b). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.54 (d, J=5.8 Hz, 2H, NHCH_2), 7.28 (m, 1H, ArH), 7.38 (m, 4H, ArH), 7.69 (m, 4H, ArH), 8.53 (t, J=5.8 Hz, 1H, NHCH$_2$). ES-MS m/z 346 MH$^+$.

4.7.3. Benzyl-(5-isobutyl-[1,3,4]thiadiazol-2-yl)-amine (11c).[15] White solid, mp 119.2–119.9 °C; ν_{max} (KBr) ν_{max} (KBr) 721, 1138, 1201, 1433, 1454, 1598, 1649, 2962, 3366 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.91 (d, J=6.5 Hz, 6H, CH(CH_3)$_2$), 1.90 (m, 1H, CH(CH$_3$)$_2$), 2.69 (d, J=7.1 Hz, 2H, CH_2CH(CH$_3$)$_2$), 4.48 (s, 2H, NHCH_2), 7.28 (m, 1H, ArH), 7.38 d, J=4.5 Hz, 4H, ArH), 8.52 (s, 1H, NHCH$_2$); ^{13}C NMR (DMSO-d_6): δ=21.8, 28.6, 38.1, 48.2, 127.3, 127.6, 128.4, 138.1, 157.3, 168.3. HR-MS (Q-TOF-ES) m/z=248.1216, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 248.1221.

4.7.4. Cyclopropylmethyl-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11d). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.27 (m, 2H, CH(CH_2CH_2)), 0.50 (m, 2H, CH(CH_2-CH_2)), 1.12 (m, 1H, CH(CH$_2$CH$_2$)), 3.21 (d, J=6.6 Hz, 2H, CH_2CH(CH$_2$CH$_2$)), 7.46 (m, 3H, ArH), 7.75 (m, 2H, ArH), 8.27 (s, 1H, NHCH$_2$). ES-MS m/z 232 MH$^+$.

4.7.5. Cyclopropylmethyl-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-amine (11e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.27 (m, 2H, CH(CH_2CH_2)), 0.50 (m, 2H, CH(CH_2CH_2)), 1.13 (m, 1H, CH(CH$_2$CH$_2$)), 3.24 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 7.61 (m, 1H, ArH), 8.27 (m, 2H, ArH), 8.32 (br s, 1H, NHCH$_2$), 8.67 (d, J=4.1 Hz, 1H, ArH), 9.01 (s, 1H, ArH). ES-MS m/z 233 MH$^+$.

4.7.6. Cyclopropylmethyl-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.49 (m, 2H, CH(CH_2CH_2)), 1.10 (m, 1H, CH(CH$_2$CH$_2$)), 3.19 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 3.81 (s, 3H, OCH_3), 7.04 (d, J=8.6 Hz, 2H, ArH), 7.69 (d, J=9.0 Hz, 2H, ArH), 8.11 (br s, 1H, NHCH$_2$). ES-MS m/z 262 MH$^+$.

4.7.7. Methyl-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11g). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.95 (s, 3H, NHCH_3), 7.47 (m, 3H, ArH), 7.77 (m, 2H, ArH), 8.10 (s, 1H, NHCH$_3$). ES-MS m/z 192 MH$^+$.

4.7.8. [5-(4-Bromo-phenyl)-[1,3,4]thiadiazol-2-yl]-methyl-amine (11h). Isolated as a pale oil; ν_{max} (KBr) 824, 976, 1067, 1154, 1202, 1399, 1497, 1553, 1678, 3283 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.95 (d, J=4.0 Hz, 3H, NHCH_3), 7.69 (m, 4H, ArH), 7.98 (s, 1H, NHCH$_3$); ^{13}C NMR (DMSO-d_6): δ=31.3, 122.7, 128.1, 130.1, 132.1, 154.6, 169.5. HR-MS (Q-TOF-ES) m/z=269.9695, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 269.9701.

4.7.9. (5-Isobutyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (11i). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.92 (d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 1.91 (m, 1H, CH(CH$_3$)$_2$), 2.70 (d, J=7.1 Hz, 2H, CH_2CH(CH$_3$)$_2$), 2.90 (s, 3H, NHCH_3) 8.34 (s, 1H, NHCH$_3$). ES-MS m/z 172 MH$^+$.

4.7.10. (4-Methoxy-benzyl)-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.74 (s, 3H, OCH_3), 4.75 (d, J=5.1 Hz, 2H, NHCH_2), 6.92 (d, J=8.5 Hz, 2H, ArH), 7.32 (d, J=8.6 Hz, 2H, ArH), 7.46 (m, 3H, ArH), 7.75 (d, J=8.1 Hz, 2H, ArH), 8.46 (t, J=5.1 Hz, 1H, NHCH$_2$). ES-MS m/z 298 MH$^+$.

4.7.11. (4-Methoxy-benzyl)-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-amine (11k). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.74 (s, 3H, OCH_3), 4.58 (d, J=5.1 Hz, 2H, NHCH_2), 6.93 (d, J=9.1 Hz, 2H, ArH), 7.32 (d, 2H, J=8.5 Hz, 2H, ArH), 7.58 (m, 1H, ArH), 8.23 (m, 1H, ArH), 8.58 (t, J=5.1 Hz, 1H, NHCH$_2$), 8.65 (m, 1H, ArH),), 8.99 (s, 1H, ArH). ES-MS m/z 299 MH$^+$.

4.7.12. (4-Methoxy-benzyl)-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) 4.44 (d, J=5.6 Hz, 2H, NHCH_2), 6.92 (d, J=8.6 Hz, 2H, ArH), 7.01 (d, 2H, J=9.1 Hz, 2H, ArH), 7.31 (d, J=8.5 Hz, 2H, ArH), 7.67 (d, J=8.5 Hz, 2H, ArH), 8.34 (t, J=5.6 Hz, 1H, NHCH$_2$). ES-MS m/z 328 MH$^+$.

4.8. Formation of hydrazine-1,2-dicarbothioamide (12)

To resin **7** (100 mg, 0.042 mmol pre-swollen in DCM was added a mixture of fmoc-isothiocyanate (60 mg, 0.21 mmol) and DIPEA (47 μL, 0.27 mmol) in DCM (2 mL) and the resulting mixture was agitated for 14 h. The resin was subsequently washed with DMF (3×) and DCM (2×).

4.9. Formation of *N*-(5-alkylamino-[1,3,4]thiadiazol-2-yl)-alkylamide (13)

General procedure. To resin **12** (100 mg, 0.042 mmol) pre-swollen in dry NMP was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol) in dry NMP (3 mL) and the mixture was agitated for 14 h at 50 °C. Excess reagent was removed by filtration and the resin was washed with NMP (2×), MeOH/THF (1:1 v/v) (2×), DCM (2×) and NMP (2×). Subsequently the resin was de-protected by treatment with NMP/piperidine (2 mL, 80:20 v/v) for 20 min, the de-protection procedure was repeated a further time. Excess reagents were removed by filtration and the resin was washed with NMP (3×) yielding the resin bound [1,3,4]thiadiazol-2-yl) amine. A solution of benzoic acid (49 mg, 0.40 mmol) in NMP/DCM (2 mL, 1:1 v/v) was added to the resin followed by DIPEA (75 μL, 0.44 mmol), DIIC (26 mg, 0.20 mmol) and a catalytic amount of DMAP (2 mg, 1.6 μmol). The mixture was agitated for 14 h before the excess reagents were removed by filtration followed by washing with NMP (3×), MeOH/THF/AcOH (10:10:1 v/v) (2×), MeOH/THF (1:1 v/v) (2×) and DCM (4×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **13**.

4.9.1. Cyclopropanecarboxylic acid [5-(4-methoxy-benzylamino)-[1,3,4]thiadiazol-2-yl]-amide (13a). White solid, mp 185.3–186.1 °C; ν_{max} (KBr) 957, 1032, 1174, 1317, 1407, 1512, 1542, 1586, 1662, 2744, 3334 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta=0.88$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 3.73 (s, 3H, OCH_3), 4.37 (s, 2H, $NHCH_2$), 6.91 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.27 (d, $J=9.1$ Hz, 2H, Ar*H*), 8.08 (s, 1H, $NHCH_2$), 12.30 (s, 1H, CON*H*); ^{13}C NMR (DMSO-d_6): $\delta=10.3$, 15.4, 49.1, 57.0, 115.8, 130.9, 132.3, 150.8, 160.5, 166.1, 173.4. HR-MS (Q-TOF-ES) $m/z=305.1076$, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 305.1072.

4.9.2. *N*-[5-(4-Methoxy-benzylamino)-[1,3,4]thiadiazol-2-yl]-benzamide (13b). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=3.74$ (s, 3H, OCH_3), 4.42 (br s, 2H, $NHCH_2$), 6.93 (d, $J=8.5$ Hz, 2H, Ar*H*), 7.31 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.53 (t, $J=8.5$ Hz, 2H, Ar*H*), 7.63 (t, $J=7.3$ Hz, 2H, Ar*H*), 8.06 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.14 (br s, 1H, $NHCH_2$), 12.5 (br s, 1H, CON*H*). ES-MS *m/z* 305 MH^+.

4.9.3. Cyclopropanecarboxylic acid (5-benzylamino-[1,3,4]thiadiazol-2-yl)-amide (13c). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.89$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 4.47 (s, 2H, $NHCH_2$), 7.32 (m, 4H, Ar*H*), 8.35 (s, 1H, $NHCH_2$), 12.38 (s, 1H, CON*H*). ES-MS *m/z* 275 MH^+.

4.9.4. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13d).[16] White solid, mp 235.9–237.1 °C; ν_{max} (KBr) 671, 694, 752, 892, 1304, 1492, 1539, 1649, 3366 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta=4.48$ (d, $J=6.1$ Hz, 2H, $NHCH_2$), 7.27 (m, 1H, Ar*H*), 7.37 (m, 4H, Ar*H*), 7.52 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.62 (t, $J=7.1$ Hz, 1H, Ar*H*), 7.89 ((t, $J=6.1$ Hz, 1H, CH_2NH), 8.05 (d, $J=7.0$ Hz, Ar*H*), 12.45 (br s, 1H, CON*H*); ^{13}C NMR (DMSO-d_6): $\delta=46.6$, 126.3, 126.8, 127.5, 127.7, 127.8, 131.8, 138.2, 163.6. HR-MS (Q-TOF-ES) $m/z=311.0961$, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 311.0967.

4.9.5. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-2-phenyl-acetamide (13e).[16] Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=3.70$ (s, 2H, PhCH_2CO), 4.43 (d, $J=5.6$ Hz, 2H, $NHCH_2$), 7.30 (m, 10H, Ar*H*), 7.82 (t, $J=5.6$ Hz, 1H $NHCH_2$), 12.17 (br s, 1H, N*H*CO). ES-MS *m/z* 325 MH^+.

4.9.6. Furan-2-carboxylic acid (5-benzylamino-[1,3,4]-thiadiazol-2-yl)-amide (13f). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=4.47$ (d, $J=5.6$ Hz, 2H, $NHCH_2$), 6.71 (m, 1H, C(OCHC*H*CH)), 7.27 (m, 1H, Ar*H*), 7.36 (m, 4H, Ar*H*), 7.57 (br s, 1H, C(OCHCHC*H*)), 7.94 (t, $J=5.6$ Hz, 1H $NHCH_2$), 7.98 (s, 1H, C(OC*H*CHCH)), 12.47 (br s, 1H, N*H*CO). ES-MS *m/z* 301 MH^+.

4.9.7. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-acetamide (13g). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.10$ (s, 3H, CH_3O), 7.47 (s, 2H, $NHCH_2$), 7.29 (m, 1H, Ar*H*), 7.35 (d, $J=4.1$ Hz, 4H, Ar*H*), 8.27 (br s, 1H, $NHCH_2$), 12.06 (br s, 1H, N*H*CO). ES-MS *m/z* 249 MH^+.

4.9.8. *N*-(5-Isobutylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13h). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.93$ (d, $J=6.5$ Hz, 6H, CH(CH_3)$_2$), 1.91 (hept, $J=6.5$ Hz, 1H, C*H*(CH_3)$_2$), 3.13 (t, $J=4.6$ Hz, 2H, CH_2NH), 7.55 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.65 (t, $J=7.1$ Hz, 2H, Ar*H*), 8.07 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.25 (br s, 1H, $NHCH_2$), 12.68 (br s, 1H, N*H*CO). ES-MS *m/z* 277 MH^+.

4.9.9. *N*-(5-Phenethylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13i). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.90$ (t, $J=7.1$ Hz, 2H, $NHCH_2CH_2$), 3.52 (t, $J=5.1$ Hz, 2H, $NHCH_2CH_2$), 7.28 (m, 5H, Ar*H*), 7.53 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.63 (t, $J=7.1$ Hz, 1H, Ar*H*), 7.74 (br s, 1H, $NHCH_2$), 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.49 (br s, 1H, N*H*CO). ES-MS *m/z* 325 MH^+.

4.9.10. Cyclopropanecarboxylic acid (5-methylamino-[1,3,4]thiadiazol-2-yl)-amide (13j). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.84$ (m, 4H, CH(CH_2CH_2)), 1.86 (m, 1H, C*H*(CH_2CH_2)), 2.80 (d, $J=4.9$ Hz, 3H, $NHCH_3$), 7.17 (q, $J=4.9$ Hz, 1H, $NHCH_3$), 12.14 (s, 1H, N*H*CO). ES-MS *m/z* 199 MH^+.

4.9.11. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13k). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.88$ (s, 3H, $NHCH_3$), 7.52 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.62 (t, $J=7.6$ Hz, 1H, Ar*H*), 7.66 (br s, 1H, $NHCH_3$), 8.04 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.54 (s, 1H, N*H*CO). ES-MS *m/z* 235 MH^+.

4.9.12. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-2-phenyl-acetamide (13l). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.88$ (s, 3H, $NHCH_3$), 3.74 (s, 2H, $COCH_2$), 7.29, (m, 5H, Ar*H*), 8.25 ($NHCH_3$), 12.50 (br s, 1H, N*H*CO). ES-MS *m/z* 249 MH^+.

4.9.13. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-acetamide (13m). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.08$ (s, 3H, $COCH_3$), 2.82 (d, $J=4.4$ Hz, 3H, $NHCH_3$), 7.21 (q, $J=4.4$ Hz, 1H, $NHCH_3$), 11.88 (s, 1H, N*H*CO). ES-MS *m/z* 173 MH^+.

4.9.14. *N*-{5-[(Tetrahydro-furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-benzamide (13n). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=1.57$ (m, 1H, CH(OCH_2-CH_2CH_2)), 1.86 (m, 2H, CH($OCH_2CH_2CH_2$), 1.97 (m 1H, CH($OCH_2CH_2CH_2$), 3.39 (dd, $J_1=6.0$ Hz, $J_2=6.8$ Hz, 2H, $NHCH_2$), 3.66 (q, $J=7.1$ Hz, 1H, CH($OCH_2CH_2CH_2$)), 3.79 (q, $J=7.1$ Hz, 1H, CH($OCH_2CH_2CH_2$)), 4.04 (m, 1H, C*H*($OCH_2CH_2CH_2$)), 7.55 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.65 (t, $J=7.1$ Hz, 2H, Ar*H*), 8.07 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.34 (d, $J=6.8$ Hz, 1H, $NHCH_2$), 12.68 (br s, 1H, N*H*CO). ES-MS *m/z* 305 MH^+.

4.9.15. Cyclopropanecarboxylic acid {5-[(furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-amide (13o). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.85$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 4.42 (d, $J=5.0$ Hz, 2H, $NHCH_2$), 6.33 (d, $J=3$ Hz, 1H, C(OCHC*H*CH)), 6.41 (q, $J=1.5$ Hz, 1H, C(OCHCHC*H*)), 7.61 (m, 1H, C(OC*H*CHCH)), 7.71 (t, $J=5.0$ Hz, 1H $NHCH_2$), 12.20 (s, 1H, CON*H*). ES-MS *m/z* 265 MH^+.

4.9.16. *N*-{5-[(Furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-benzamide (13p). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=4.47$ (d, $J=5.0$ Hz, $NHCH_2$), 6.35

(d, $J=3.0$ Hz, 1H, C(OCHC*H*CH)), 6.42 (m, 1H, C(OCHCHC*H*)), 7.53 (m, 2H, Ar*H*), 7.62 (m, 2H, Ar*H* and C(OC*H*CHCH)), 7.82 (t, $J=5.0$ Hz, 1H, N*H*CH_2) 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.49 (s, 1H, N*H*CO). ES-MS *m/z* 301 MH^+.

4.9.17. *N*-{5-[(Furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-2-phenyl-acetamide (13q). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.71$ (s, 2H, COCH_2), 4.42 (d, $J=5.6$ Hz, NHCH_2), 6.32 (d, $J=3.0$ Hz, 1H, C(OCHC*H*CH)), 6.40 (m, 1H, C(OCHCHC*H*)), 7.31 (m, 5H, Ar*H*), 7.60 (m, 1H, 1H, C(OC*H*CHCH)), 7.74 (t, $J=5.6$ Hz, NHCH$_2$), 12.20 (s, 1H, N*H*CO). ES-MS *m/z* 315 MH^+.

4.9.18. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-benzamide (13r). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.22$ (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.08 (m, 1H, C*H*(CH_2CH_2)), 3.13 (t, $J=6.8$ Hz, 2H, NHCH_2*c*Pr), 7.51 (m, 3H Ar*H*), 7.61 (t, $J=6.8$ Hz, 1H, CH$_2$N*H*), 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.42 (br s, 1H, CON*H*). ES-MS *m/z* 275 MH^+.

4.9.19. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-2-phenyl-acetamide (13s). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.19$ (m, 2H, CH(CH_2CH_2)), 0.43 (m, 2H, CH(CH_2CH_2)), 1.03 (m, 1H, C*H*(CH_2CH_2)), 3.08 (t, $J=6.0$ Hz, 2H, NHCH_2*c*Pr), 3.69 (s, 2H, CH_2Ph) 7.29 (m, 5H Ar*H*), 7.38 (t, $J=6.0$ Hz, 1H, CH$_2$N*H*), 12.11 (s, 1H, CON*H*). ES-MS *m/z* 289 MH^+.

4.9.20. Furan-2-carboxylic acid [5-(cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-amide (13t). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.24$ (m, 2H, CH(CH_2-CH_2)), 0.51 (m, 2H, CH(CH_2CH_2)), 1.10 (m, 1H, C*H*(CH$_2$-CH$_2$)), 3.16 (t, $J=6.6$ Hz, 2H, NHCH_2*c*Pr), 6.73 (m, 1H, Ar*H*), 7.59 (m, 1H, Ar*H*), 8.01 (m, 1H, Ar*H*) 8.11 (br s, 1H, CH$_2$N*H*), 12.66 (s, 1H, CON*H*). ES-MS *m/z* 265 MH^+.

4.9.21. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4] thiadiazol-2-yl]-acetamide (13u). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.21$ (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, C*H*(CH$_2$CH$_2$)), 2.08 (s, 3H, CH_3CO) 3.10 (t, $J=6.6$ Hz, 2H, NHCH_2*c*Pr), 7.35 (t, $J=6.6$ Hz, 1H, CH$_2$N*H*), 11.84 (s, 1H, CON*H*). ES-MS *m/z* 213 MH^+.

4.9.22. *N*-{5-[(Pyridin-4-ylmethyl)-amino]-[1,3,4] thiadiazol-2-yl}-benzamide (13v). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=4.76$ (d, $J=4.6$ Hz, 2H CH_2), 7.53 (m, 3H, Ar*H*), 7.82 (d, $J=6.7$ Hz, 2H, Ar*H*), 8.06 (d, $J=7.0$ Hz, 2H, Ar*H*), 8.24 (m, 1H, CH$_2$N*H*), 8.78 (d, $J=6.7$ Hz, 2H, Ar*H*), 11.84 (s, 1H, CON*H*). ES-MS *m/z* 312 MH^+.

4.9.23. 2-Phenyl-*N*-{5-[(pyridin-4-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-acetamide (13x). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.72$ (s, 2H, COCH_2) 4.71 (d, $J=4.3$ Hz, CH_2NH), 7.31 (m, 6H, Ar*H*), 7.78 (d, $J=6.0$ Hz, Ar*H*), 8.16 (m, 1H, CH$_2$N*H*), 8.77 (d, $J=6.6$ Hz, Ar*H*), 12.27 (s, 1H, CON*H*). ES-MS *m/z* 326 MH^+.

4.10. Formation of semicarbazide (14)

Typical procedure. Resin **5** (1.0 g, 0.42 mmol) swollen in DCM (15 mL) and DIPEA (2 mL) was agitated for 10 min before a solution of triphosgene (380 mg, 1.3 mmol) in DCM (10 mL) was added. The resulting mixture was agitated for 5 h before excess reagents were removed by filtration and the resin was washed with DCM (3×). A solution of hydrazine hydrate (210 mg, 4.2 mmol) in DMSO (15 mL) was added and the mixture was agitated for 14 h before the resin was filtered and washed with DMSO (3×), MeOH/THF/AcOH (10:10:1, v/v) (2×), MeOH/THF (1:1, v/v) (2×) and DCM (4×). The resin was dried in vacuo overnight at 40 °C to yield resin bound semicarbazide **14**.

4.11. Formation of carbamoyl thiosemicarbazide (15)

Typical procedure. A solution of isothiocyanate (0.21 mmol) dissolved in DCM (2 mL) and DIPEA (50 μL, 0.29 mmol) was added to resin **14** and the mixture was agitated for 6 h. Excess reagents were removed by filtration and the resin was washed with DCM (2×), NMP (3×), MeOH/THF (1:1, v/v) (2×) and DCM (3×) yielding resin bound carbamoyl thiosemicarbazide **15**.

4.12. Formation of *N*,*N*-dialkyl-[1,3,4]oxadiazoles-2,5-diamine (16)

Typical procedure. To resin **15** (100 mg, 0.042 mmol) preswollen in dry NMP was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol,) in dry NMP (3 mL) and the mixture was agitated for 14 h at 60 °C. Excess reagents were removed by filtration and the resin was washed with NMP (2×), MeOH/THF (1:1, v/v) (2×) and DCM (4×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **15**.

4.12.1. *N*-Benzyl-*N′*-(4-methoxy-benzyl)-[1,3,4]oxadiazole-2,5-diamine (16a). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.72$ (s, 3H, OCH_3), 4.16 (d, $J=6.1$ Hz, 2H, NHCH_2), 4.24 (d, $J=6.1$ Hz, 2H, NHCH_2), 6.87 (d, $J=9.1$ Hz, 2H, Ar*H*), 7.24 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.32 (m, 5H, Ar*H*), 7.40 (t, $J=6.1$ Hz, 1H, N*H*), 7.48 (t, $J=6.1$ Hz, 1H, N*H*). ES-MS *m/z* 311 MH^+.

4.12.2. *N*-Cyclopropylmethyl-*N′*-(4-methoxy-benzyl)-[1,3,4]oxadiazole-2,5-diamine (16b). White solid, mp 104.7–105.2 °C; ν_{max} (KBr) 823, 1034, 1177, 1252, 1302, 1515, 1569, 1660, 2927, 3298 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta=0.23$ (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2-CH_2)), 1.04 (m, 1H, C*H*(CH$_2$CH$_2$)), 3.01 (m, 2H, CH_2-CH(CH$_2$CH$_2$)), 3.74 (s, 3H, OCH_3), 4.25 (br s, 2H, NHCH_2), 6.91 (d, $J=9.1$ Hz, 2H, Ar*H*), 7.29 (d, $J=7.4$ Hz, 2H, Ar*H*), 7.52 (br s, 1H, N*H*), 7.57 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): $\delta=3.39$, 10.3, 45.3, 47.1, 55.1, 113.8, 129.0, 129.8, 156.8, 158.4, 158.6. HR-MS

(Q-TOF-ES) m/z=275.1503, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 275.1508.

4.12.3. *N*,*N*′-Dibenzyl-[1,3,4]oxadiazole-2,5-diamine (16c). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.32 (d, J=6.1 Hz, 4H, NHCH_2), 7.25 (m, 2H, Ar*H*), 7.35 (m, 8H, Ar*H*), 8.61 (br s, 2H, N*H*). ES-MS m/z 281 MH^+.

4.12.4. *N*-Benzyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16d). White solid, mp 134.8–135.9 °C; ν_{max} (KBr) 697, 1136, 1201, 1263, 1359, 1452, 1598, 1680, 2983, 3170 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.82 (t, J=7.6 Hz, 2H, PhCH_2CH_2), 3.28 (m, 2H, PhCH_2CH_2), 4.26 (d, J=6.3 Hz, PhCH_2NH), 7.27 (m, 11H, Ar*H* and N*H*), 8.17 (t, J=6.3 Hz 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ=34.5, 43.9, 45.8, 126.0, 126.9, 127.3, 128.2, 128.2, 128.6, 138.8, 139.1, 157.8, and 157.9. HR-MS (Q-TOF-ES) m/z=295.1553, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 295.1559.

4.12.5. *N*-Benzyl-*N*′-cyclopropylmethyl-[1,3,4]oxadiazole-2,5-diamine (16e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.22 (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 2.99 (m, 2H, CH_2CH(CH_2CH_2)), 4.31 (d, J=6.1 Hz, 2H, NHCH_2Ph), 7.30 (m, 5H, Ar*H*), 8.32 (br s, 1H, N*H*), 8.43 (br s, 1H, N*H*). ES-MS m/z 245 MH^+.

4.12.6. *N*-Cyclopropylmethyl-*N*′-ethyl-[1,3,4]oxadiazole-2,5-diamine (16f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 1.14 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.00 (m, 2H, NHCH_2CH_2), 3.15 (m, 2H, CH_2CH(CH_2CH_2)), 8.20 (br s, 1H, N*H*), 8.37 (br s, 1H, N*H*). ES-MS m/z 183 MH^+.

4.12.7. *N*-Cyclopropylmethyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16g).[15] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 2.85 (t, J=7.2 Hz, 2H, PhCH_2CH_2), 3.00 (m, 2H, CH_2-CH(CH_2CH_2)), 3.35 (m, 2H, PhCH_2CH_2), 7.25 (m, 5H, Ar*H*), 8.31 (br s, 1H, N*H*), 8.37 (br s, 1H, N*H*). ES-MS m/z 259 MH^+.

4.12.8. *N*-Benzyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16h).[17] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.33 (d, J=6.1 Hz, 2H, NHCH_2), 6.91 (t, J=7.1 Hz, 1H, Ar*H*), 7.28 (m, 3H, Ar*H*), 7.37 (m, 4H, Ar*H*), 7.45 (d, J=7.6 Hz, 2H, Ar*H*), 7.82 (t, J=6.1 Hz, 1H, N*H*CH_2), 9.95 (s, 1H, PhN*H*). ES-MS m/z 266 MH^+.

4.12.9. *N*-Ethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16i).[17] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=1.18 (t, J=7.6 Hz, 3H, CH_2CH_3), 3.20 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 6.95 (t, J=7.6 Hz, 1H, Ar*H*), 7.31 (t, J=8.6 Hz, 2H, Ar*H*), 7.44 (d, J=7.6 Hz, 2H, Ar*H*), 8.07 (br s, 1H, N*H*CH_2), 10.21 (s, 1H, PhN*H*). ES-MS m/z 205 MH^+.

4.12.10. *N*-Phenethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.87 (t, J=7.0 Hz, 2H, CH$_2$CH_2Ph), 3.45 (m, 2H, CH_2CH$_2$Ph), 6.92 (t, J=7.5 Hz, 1H, Ar*H*), 7.29 (m, 9H, Ar*H* and N*H*CH_2), 7.47 (d, J=7.6 Hz, 2H, Ar*H*), 9.91 (s, 1H, PhN*H*). ES-MS m/z 281 MH^+.

4.12.11. *N*-Cyclopropylmethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16k). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, C*H*(CH$_2$CH$_2$)), 3.01 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 6.93 (t, J=7.6 Hz, 1H, Ar*H*), 7.29 (t, J=8.4 Hz, 2H, Ar*H*), 7.44 (d, J=7.6 Hz, 2H, Ar*H*), 7.91 (br s, 1H, N*H*CH$_2$), 10.10 (s, 1H, PhN*H*). ES-MS m/z 231 MH^+.

4.12.12. *N*-Methyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.76 (d, J=2.0 Hz, NHCH_3), 2.84 (t, J=7.1 Hz, 2H, PhCH_2CH$_2$), 3.34 (m, 2H, PhCH$_2$CH_2), 7.25 (m, 5H, Ar*H*), 8.17 (br s, 1H, N*H*), 8.24 (s, 1H, N*H*). ES-MS m/z 219 MH^+.

4.12.13. *N*-Cyclopropylmethyl-*N*′-methyl-[1,3,4]oxadiazole-2,5-diamine (16m). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH$_2$CH$_2$)), 2.76 (s, 3H, NHCH_3), (3.00 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 8.17 (br s, 1H, N*H*), 8.29 (br s, 1H, N*H*). ES-MS m/z 169 MH^+.

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