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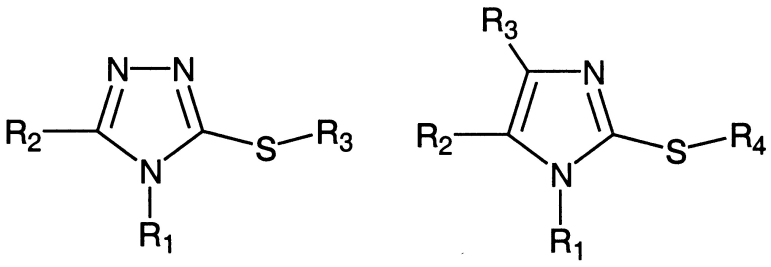

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Rapid Parallel Synthesis of Combinatorial Libraries of Substituted 3-Thio-1,2,4-triazoles and 2-Thioimidazoles

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Combinatorial libraries of substituted 3-thio-1,2,4-triazoles and 2-thioimidazoles were synthesized in good yield by alkylation of the products via the reaction of isothiocyanates and carboxylic acid hydrazides or β-aminoketones, respectively. A total of 275 3-thio-1,2,4-triazoles and 283 2-thioimidazoles were synthesized out of the attempted 288 in each case. Most the yields were between 45% and 98%, and all the compounds synthesized were purified to >85% purity. Variations in yields revealed no definitive trends and were mainly attributed to bulky alkylating agents used and the plate well location of the reaction mixtures.

Substituted 1,2,4-triazole and imidazole moieties can be found in a vast number of compounds displaying biological activity.[1−5] For example, substituted 2-thioimidazoles are present in compounds that possess antiasthmatic,[6] antiinflammatory,[7] antiulcerative,[8] and antithrombotic[9] activities. Compounds possessing 3-thio-1,2,4-triazoles have been shown to act as angiotensin II antagonists[10,11] and dopamine D3 antagonists.[12,13]

As part of an ongoing drug discovery program, we required a procedure to rapidly synthesize and purify combinatorial libraries of 2-thioimidazoles and 3-thio-1,2,4-triazoles.

Compounds of the type shown in Figure 1 have been synthesized in the past via a variety of methods.[14−18] Although most of these routes were satisfactory for the synthesis of small numbers of compounds, we required a synthetic method for the synthesis of 2-thioimidazoles and 3-thio-1,2,4-triazoles that could be amenable to a high-throughput parallel synthesis protocol. The method should be efficient and convergent and should require minimum manipulation and modification.

Our main criteria were that the entire synthesis would be carried out in a 96-well setup in an automated format and the final products would be generated in high abundance and good yields.

The route selected for the syntheses of 3-thio-1,2,4-triazole libraries is shown in Scheme 1. Three points of diversity would thus be incorporated into the final library through the use of substituted isothiocyanates (R_1), acyl hydrazides (R_2), and alkyl halides (R_3). Simple variation of the acyl hydrazide to a β-aminoketone, as shown in Scheme 2, would yield a combinatorial library of 2-thioimidazoles, with four positions of diversity, via the same process.

The syntheses of the two libraries were thus carried out in glass microtiter plates on a Genesis Gemini Tecan platform. Four isothiocyanates were reacted with two acyl hydrazides and two β-amino ketones to yield 3-thio-1,2,4-triazoles and 2-thioimidazoles, respectively. The synthesis was completed via addition of base and the desired 36 alkyl halides. The compounds were directly purified using a mass-triggered preparative LC/MS (reverse phase).[20,21]

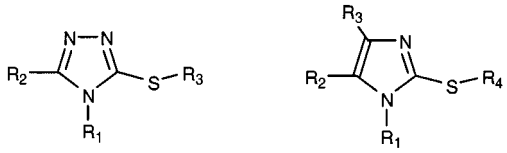
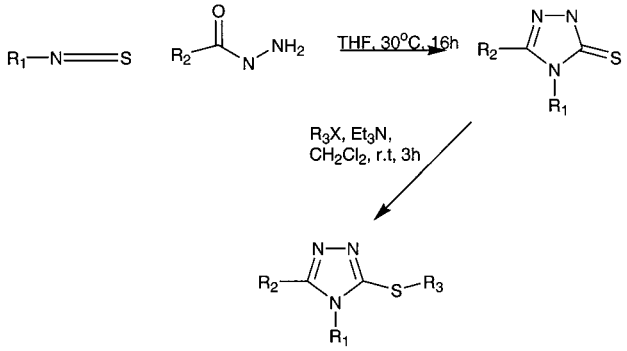


Figure 1. Substituted 3-thio-1,2,4-triazole (a) and substituted 2-thioimidazole (b).

Scheme 1. Synthesis Route for 3-Thio-1,2,4-triazoles



Scheme 2. Synthesis Route for 2-Thioimidazoles

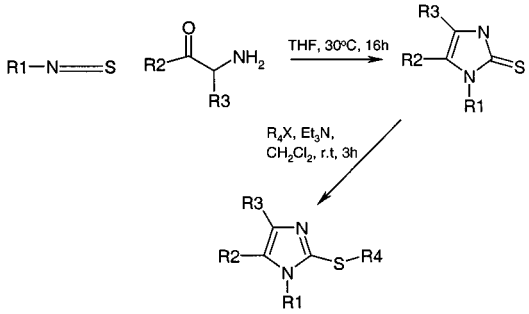


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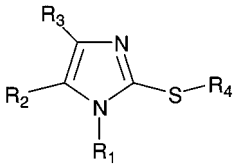
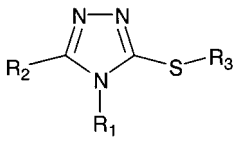
Table 1. Final Overall Yields of Substituted 2-Thioimidazoles and Substituted 3-Thio-1,2,4-triazoles





compd	R_1	R_2	R_3[a]	R_4	yield, %
1	cyclopropyl	Ph	H	CH_2CHCH_2	80
2	cyclopropyl	Ph	H	CH_2CN	81
3	cyclopropyl	4-MeOPh	H	4-Me−Bz	78
4	cyclopropyl	Ph	H	2-CH_2−naphthyl	71
5	cyclopropyl	4-MeOPh	H	2-CH_2−tetrahydrofuran	67
6	cyclopropyl	Ph	H	$(CH_2)_2CH{=}CH_2$	81
7	cyclopropyl	4-MeOPh	H	2-Cl−Bz	98
8	CH_3	4-MeOPh	H	4-SO_2CH_3−Bz	75
9	CH_3	4-MeOPh	H	CH_2CCCH_3	97
10	CH_3	Ph	H	3,4-Cl−Bz	94
11	CH_3	Ph	H	CH_2−2-naphthyl	80
12	Ph	Ph	H	$(CH_2)_2$−3-indole	71
13	Ph	Ph	H	$CH_2CCH_2CH_3$	75
14	Ph	4-MeOPh	H	$CH_2CHCHCH_3$	73
15	Ph	Ph	H	2-NO_2−Bz	70
16	3-MeO−Ph	4-MeOPh	H	CH_2−2-NO_2−furyl	75
17	3-MeO−Ph	Ph	H	$(CH_2)_2N(Et)_2$	60
18	3-MeO−Ph	Ph	H	CH_2−2-1,4-benzodioxan	53
19	3-MeO−Ph	Ph	H	1-$(CH_2)_2$−pyrrole	96

compd	R_1	R_2	R_3[a]	yield, %
20	cyclopropyl	Bz	3,5-diF−Bz	90
21	cyclopropyl	Bz	4-SO_2CH_3−Bz	60
22	cyclopropyl	Bz	2-F−Bz	95
23	cyclopropyl	Bz	$(CH_2)_3$ CH CH_2	68
24	cyclopropyl	Bz	CH_2−2-naphthyl	65
25	cyclopropyl	Bz	3-Cl−Bz	89
26	CH_3	Bz	$(CH_2)_2$−3-indole	54
27	CH_3	*n*-Pr	$(CH_2)_2CN$	81
28	CH_3	*n*-Pr	$(CH_2)_2N(Et)_2$	45
29	CH_3	Bz	$(CH_2)_3CH_3$	77
30	Ph	Bz	$(CH_2)_2$−3-indole	58
31	Ph	*n*-Pr	CH_2−2-1,4-benzodioxan	79
32	Ph	*n*-Pr	$(CH_2)_2OEt$	58
33	Ph	*n*-Pr	$(CH_2)_2CHEt$	67
34	3-MeO−Ph	*n*-Pr	$(CH_2)_2O(CH_2)_2OCH_3$	74
35	3-MeO−Ph	Bz	CH_2−2-tetrahydrofuran	88
36	3-MeO−Ph	Bz	$CH_2CCH_2CH_3$	81
37	3-MeO−Ph	*n*-Pr	$(CH_2)_2O$(4-Br−Ph)	71
38	3-MeO−Ph	*n*-Pr	1-$(CH_2)_2$−pyrrole	57

[a] Variations in R_3 were carried out but not shown here because they are of a confidential nature.

Of the 576 compounds attempted, 558 of the desired products were isolated in multimilligram quantities and greater than 85% purity. On average, a total of more than 10 mg was obtained and overall yields ranged from 45% to 98% (Table 1). Thus, the procedure was easily translated from individual reactions to library preparation, which had been a key objective.

Conclusion

A facile parallel synthesis technique has been developed for the synthesis of a diverse set of 3-thio-1,2,4-triazoles and 2-thioimidazoles in excellent yield. This work differs from the previously described literature methods not utilizing parallel synthesis methodology in that it allows the use of a large variety of R groups in all the diversity positions while also providing the most efficient route for synthesizing both 3-thio-1,2,4-triazoles and 2-thioimidazoles in comparable yields with minor changes.

In previous literature procedures, different experimental conditions were used to obtain the best results for the synthesis of these two classes of compounds or their intermediates.[22−29] Use of this method requires no significant changes, and the yields and purities are excellent in both cases. Almost all the R groups utilized, in all the diversity positions, worked very well with this method. A total of 275 3-thio-1,2,4-triazoles and 283 2-thioimidazoles were synthesized out of the 288 attempted in each case. Overall, the yields of 3-thio-1,2,4-triazoles and 2-thioimidazoles were very comparable. Variations in the isothiocyanates utilized produced similar yield differences in both classes. Increasing the bulk of the R_1 group slightly decreased yields. Lower yields, in both classes, were obtained in cases where the alkylating group used contained a larger, hence bulkier, alkyl chain. No other obvious monomer trends were observed that reflect the yield differences. Upon closer observation, it was noticed that the lower yielding reaction mixtures within specific sets appeared to be located at the edges of the 96-well plates. A possible conclusion can hence be reached as to the reason these specific products were produced in lower yield. The reagent dispensation to these specific wells might have differed from the rest of the plate and they might have been heated unevenly. Hence, the desired intermediates might not have been fully formed, resulting in a difference in the observed yields.

This work represents our initial efforts into preparing libraries of these types of interesting heterocycles. Additional efforts on related heterocyclic combinatorial libraries and their biological activity will be reported shortly.

Experimental Section

All reagents and glass microtiter plates were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were used directly.

Library Synthesis. General Procedure for the Synthesis of Substituted 2-Thioimidazoles in a 96-Well Format. Each isothiocyanate (7.5 mmol) and the corresponding β-amino ketone (15 mmol) were dissolved to a 10 mM concentration in ethanol. The isothiocyanate and the respective β-amino ketone components were combined in a 1:1 ratio in their respective wells, in the presence of triethylamine (3.75 mmol), via the use of the Genesis Gemini Tecan platform. The plates were then sealed, removed from the workstation, and refluxed at 80 °C overnight. Complete synthesis of the intermediates in each case was confirmed by LC/MS analysis. This was carried out using an analytical YMC ODS-A reversed-phase column (4.6 mm × 50 mm) via use of a 10−99% gradient of 0.05% TFA in water/0.035% TFA in acetonitrile. The plate was then evaporated

to dryness via a GeneVac HT-12 at 40 °C for 2 h. The contents of the plates were then resuspended in 2 mL of dichloromethane per well, and the final alkylations were carried out via the addition of triethylamine (1.5 equiv; 0.156 mmol) and the 36 desired alkyl halides (1.2 equiv each; 0.125 mmol). The reaction mixtures were then shaken at room temperature for 3 h. Analysis of the crude products via analytical LC/MS indicated completion of the reaction. The reaction mixtures were once again evaporated to dryness via a GeneVac HT-12 at 45 °C for 3 h, resuspended in 1 mL of 1:1 DMSO/MeOH, filtered, and directly purified using a mass-triggered preparative reversed-phase LC/MS.[20,21] The final purification was carried out using a semipreparative YMC ODS-A reversed-phase column (20 mm × 50 mm, particle size S-5) via use of a 10−99% gradient of 0.05% TFA in water/0.035% TFA in acetonitrile (flow rate of 35 mL/min) on a Shimadzu HPLC system with an API150EX single quadropole mass spectrometer. The purification throughput was 160 compounds per instrument per day. The final purified compounds were analyzed to determine their final purity by analytical LC/MS.

General Procedure for the Synthesis of Substituted 3-Thio-1,2,4-triazoles in a 96-Well Format. Each isothiocyanate (3.75 mmol) and the corresponding acylhydrazine (3.75 mmol) were dissolved to a 10 mM concentration in ethanol. The isothiocyanate and the respective acylhydrazine components were combined in a 1:1 ratio in their respective wells, in the presence of triethylamine (3.75 mmol), via the use of the Genesis Gemini Tecan platform. The plates were then sealed, removed from the workstation, and refluxed at 80 °C overnight. Complete synthesis of the intermediates in each case was confirmed by LC/MS analysis. This was carried out using an analytical YMC ODS-A reversed-phase column (4.6 mm × 50 mm) via use of a 10−99% gradient of 0.05% TFA in water/0.035% TFA in acetonitrile. A 2 M sodium hydroxide solution was added to each well (0.208 mmol). The plate was resealed and heated at 80 °C for a further 5 h. Once the final intermediates had been formed, the plate contents were evaporated to dryness via use of a GeneVac HT-12 system at 40 °C for 2h. The contents of the plates were then resuspended in 2 mL of dichloromethane per well, and the final alkylations were carried out via the addition of triethylamine (1.5 equiv; 0.156 mmol) and the 36 desired alkyl halides (1.2 equiv each; 0.125 mmol). The reaction mixtures were then shaken at room temperature for 3 h. Analysis of the crude products via analytical LC/MS indicated completion of the reaction. The reaction mixtures were once again evaporated to dryness via a GeneVac HT-12 at 45 °C for 3 h, resuspended in 1 mL of 1:1 DMSO/MeOH, filtered, and directly purified using a mass-triggered preparative reversed-phase LC/MS.[20,21] The final purification was carried out using a semipreparative YMC ODS-A reversed-phase column (20 mm × 50 mm, particle size S-5) via use of a 10−99% gradient of 0.05% TFA in water/0.035% TFA in acetonitrile (flow rate of 35 mL/min) on a Shimadzu HPLC system with an API 150EX single quadropole mass spectrometer. The purification throughput was 160 compounds per instrument per day. The final purified compounds were analyzed to determine their purity by analytical LC/MS.

Representative Data and Spectra for the Final Substituted 2-Thioimidazoles and Substituted 3-Thio-1,2,4-triazoles (1-Cyclopropyl-5-phenyl-1*H*-imidazol-2-ylsulfanyl)acetonitrile (Compound 2): yield 81%; *m*/*z* $[M + H]^+$ 256; 95% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.56−7.18 (m, J = 6.4 Hz, J = 5.2 Hz, 6H), 4.29 (s, 2H), 3.01 (m, 1H), 1.15−0.90 (m, 4H).

1-Cyclopropyl-5-(4-methoxyphenyl)-2-(4-methylbenzylsulfanyl)-1*H*-imidazole (3): yield 78%; *m*/*z* $[M + H]^+$ 351; 95% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.47 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.14 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 4.42 (s, 2H), 3.83 (s, 3H), 2.52−2.48 (m, 1H, hidden under solvent peak), 2.31 (s, 3H), 1.05−0.60 (m, 4H).

2-But-3-enylsulfanyl-1-cyclopropyl-5-phenyl-1*H*-imidazole (6): yield 81%; *m*/*z* $[M + H]^+$ 271; 93% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.55−7.35 (m, J = 6.8, 8.0 Hz, 5H), 7.15 (s, 1H), 6.05 (m, 1H), 5.30 (dd, J = 17.2 Hz, 1H), 5.11 (d, J = 9.6 Hz, 2H), 3.86 (d, J = 6.8 Hz, 2H), 2.52−2.48 (m, 1H, hidden under solvent peak), 0.99−0.65 (m, 4H).

2-(2-Chlorobenzylsulfanyl)-1-cyclopropyl-5-(4-methoxyphenyl)-1*H*-imidazole (7): yield 98%; *m*/*z* $[M + H]^+$ 371; 87% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.51−7.29 (double multiplet, J = 10.4, 7.6 Hz, 6H), 7.19 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 4.52 (s, 2H), 3.82 (s, 3H), 2.52−2.48 (m, 1H, hidden under solvent peak), 1.05−0.65 (m, 4H).

2-(4-Methanesulfonylbenzylsulfanyl)-5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (8): yield 75%; *m*/*z* $[M + H]^+$ 389; 85% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.87 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.19 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.42 (s, 2H), 3.83 (s, 3H), 3.49 (s, 3H), 3.18 (s, 3H).

2-But-2-ynylsulfanyl-5-(4-methoxyphenyl)-1-methyl-1*H*-imidazole (9): yield 97%; *m*/*z* $[M + H]^+$ 273; 92% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.42 (d, J = 8.8 Hz, 2H), 7.18 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 3.67 (s, 3H), 3.60 (s, 2H), 1.79 (s, 3H).

1-Methyl-2-(naphthalen-2-ylmethylsulfanyl)-5-phenyl-1*H*-imidazole (11): yield 80%; *m*/*z* $[M + H]^+$ 331; 93% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.88−7.75 (m, J = 8.4 Hz, 4H), 7.62−7.60 (d, J = 8.4 Hz, 1H), 7.49−7.20 (m, J = 8.0, 8.4 Hz, 7H), 7.18 (s, 1H), 4.63 (s, 2H), 3.65 (s, 3H)

3-[2-(1,5-Diphenyl-1*H*-imidazol-2-ylsulfanyl)ethyl]-1*H*-indole (12): yield 71%; *m*/*z* $[M + H]^+$ 396; 90% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO/H_2O (6:6:1)) δ 7.55 (d, J = 8.0 Hz, 2H), 7.49−7.09 (three sets of multiplets, J = 8.0, 8.4 Hz, 7.4 Hz, 13H), 7.01 (s, 1H), 3.07 (m, 4H, partially hindered by H_2O peak).

1-(3-Methoxyphenyl)-2-(5-nitrofuran-2-ylmethylsulfanyl)-5-phenyl-1*H*-imidazole (16): yield 75%; *m*/*z* $[M + H]^+$ 438; 89% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.45 (d, 1H), 7.34−7.29 (dd, J = 8.4 Hz, 2H), 7.28 (s, 1H), 7.03−7.00 (m, J = 8.4 Hz, 3H), 6.82 (d, J = 8.4 Hz, 2H), 6.75 (m, J = 8.4 Hz, 1H), 6.65 (s, 1H), 4.39 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H).

2-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethylsulfanyl)-1-(3-methoxyphenyl)-5-phenyl-1*H*-imidazole (18): yield 53%; *m/z* $[M + H]^+$ 431; 85% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO/H_2O (6:6:1)) δ 7.39−7.03 (three sets of multiplets, 10H), 6.86−6.70 (dd, J = 8.4,12 Hz, 4H), 4.50 (m, 1H), 4.30 (m, 2H), 3.73 (s, 3H), 3.34 (d, hindered by H_2O peak, 3H).

1-(3-Methoxyphenyl)-5-phenyl-2-(2-pyrrol-1-yl-ethylsulfanyl)-1*H*-imidazole (19): yield 96%; *m/z* $[M + H]^+$ 376; 95% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO/H_2O (6:6:1)) δ 7.40−7.37 (m, J = 8.0, 8.4 Hz, 3H), 7.27−7.20 (m, J = 7.2, 8.4 Hz, 2H), 7.14 (dd, J = 6.8 Hz, 1H), 7.05 (dd, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.82 (dd, J = 8.0 Hz, 2H), 6.74 (broad d, 2H), 5.98 (broad dd, 2H), 4.20 (t, J = 6.8 Hz, 2H), 3.74 (s, 3H), 3.40 (t, hindered by H_2O peak, 2H).

3-Benzyl-4-cyclopropyl-5-(3,5-difluorobenzylsulfanyl)-4*H*-[1,2,4]triazole (20): yield 90%; *m/z* $[M + H]^+$ 358; 90% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.32 (dd, J = 8.4 Hz, 2H), 7.29 (dd, J = 8.4 Hz, 1H), 7.22 (dd, J = 8.4 Hz, 2H), 7.18 (dd, J = 8.4, 8.8 Hz, 2H), 7.08 (dd, J = 8.4, 8.8 Hz, 1H), 4.44 (s, 2H), 4.18 (s, 2H), 2.52−2.48 (m, 1H, hidden under solvent peak), 1.05−0.65 (m, 4H).

3-Benzyl-4-cyclopropyl-5-(4-methanesulfonylbenzylsulfanyl)-4*H*-[1,2,4]triazole (21): yield 60%; *m/z* $[M + H]^+$ 400; 87% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.85 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.32 (m, J = 7.2 Hz, 3H), 7.24−7.19 (dd, J = 7.6, 9.2 Hz, 3H), 4.53 (s, 2H), 4.17 (s, 2H), 3.17 (s, 3H), 2.78 (m, hidden under solvent peak, 1H), 0.95−0.65 (m, 4H).

3-Benzyl-4-cyclopropyl-5-pent-4-enylsulfanyl-4*H*-[1,2,4]-triazole (23): yield 68%; *m/z* $[M + H]^+$ 300; 85% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.56 (dd, J = 7.6 Hz, 2H), 7.45 (dd, J = 7.6 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 5.72 (m, J = 10, 15 Hz, 1H), 5.07 (dd, J = 17 Hz, 1H), 5.01 (dd, J = 10 Hz, 1H), 3.99 (s, 2H), 3.18 (t, 2H), 2.74 (quintet, 1H), 2.10−1.85 (m, J = 7.2 Hz, 2H), 1.82−1.79 (quintet, J = 7.2, 7.6 Hz, 2H), 1.01−0.65 (m, 4H).

3-Benzyl-4-cyclopropyl-5-(naphthalen-2-ylmethylsulfanyl)-4*H*-[1,2,4]triazole (24): yield 65%; *m/z* $[M + H]^+$ 372; 99% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.88−7.83 (m, J = 8.0, 8.4 Hz, 3H), 7.58−7.48 (m, J = 8.0, 8.4 Hz, 3H), 7.29−7.20 (m, J = 8.0, 8.4 Hz, 3H), 7.15−7.07 (m, J = 8.0, 8.4 Hz, 3H), 4.59 (s, 2H), 4.17 (s, 2H), 2.78 (quintet, 1H), 0.95−0.62 (m, 4H).

3-Benzyl-5-(3-chlorobenzylsulfanyl)-4-cyclopropyl-4*H*-[1,2,4]triazole (25): yield 89%; *m/z* $[M + H]^+$ 356; 95% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.32−7.12 (three sets of multiplets, J = 7.6, 8.0, 8.4 Hz, 9H), 4.42 (s, 2H), 4.17 (s, 2H), 2.78 (quintet, 1H), 1.01−0.73 (m, 4H).

3-[2-(5-Benzyl-4-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-ethyl]-1*H*-indole (26): yield 54%; *m/z* $[M + H]^+$ 349; 95% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.50−7.47 (m, J = 7.8 Hz, 4H), 7.25−7.17 (m, J = 7.8 Hz, 4H), 7.13 (t, J = 7.8 Hz, 1H), 6.80 (broad s, 1H), 3.80 (s, 2H), 3.60−3.30 (two s, hidden by solvent peak, 5H).

(4-Methyl-5-propyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)acetonitrile (27): yield 81%; *m/z* $[M + H]^+$ 225; 96% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 3.50 (s, 3H), 3.13 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 7.8 Hz, 2H), 1.96 (quintet, J = 6.8 Hz, 2H), 1.71 (m, J = 7.6 Hz, 2H), 0.98 (s, 3H).

3-[2-(5-Benzyl-4-phenyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-ethyl]-1*H*-indole (30): yield 58%; *m/z* $[M + H]^+$ 411; 86% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.55 (m, J = 7.8 Hz, 5H), 7.25−7.17 (m, J = 7.8 Hz, 6H), 7.10−6.85 (m, J = 7.8 Hz, 4H), 4.00 (s, 2H), 3.62−3.23 (s, hidden by solvent peak, 2H).

3-(2,3-Dihydrobenzo[1,4]dioxin-2-ylmethylsulfanyl)-4-phenyl-5-propyl-4*H*-[1,2,4]triazole (31): yield 79%; *m/z* $[M + H]^+$ 368; 90% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO/H_2O (6:6:1)) δ 7.62−7.53 (s, 5H), 6.90−6.80 (m, J = 6.4 Hz, 4H), 4.48 (m, J = 4 Hz, 1H), 4.35 (dd, J = 2.4, 12 Hz, 1H), 4.00 (dd, J = 6.8, 4.8 Hz, 1H), 3.60−3.25 (t, hidden by H_2O peak, 2H), 2.56−2.50 (t, hidden by solvent peak, 2H), 1.55 (m, J = 7.6 Hz, 2H), 0.85 (t, J = 7.6 Hz, 3H).

3-[2-(2-Methoxyethoxy)ethylsulfanyl]-4-(3-methoxyphenyl)-5-propyl-4*H*-[1,2,4]triazole (34): yield 74%; *m/z* $[M + H]^+$ 352; 88% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.54 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 8.0 Hz, 1H), 7.05 (s, 1H), 6.96 (dd, J = 8 Hz, 1H), 3.82 (s, 3H), 3.66 (t, J = 6.4 Hz, 2H), 3.52 (t, J = 4, 6 Hz, 4H), 3.12−3.43 (t and s, hidden by H_2O peak, 5H), 2.55 (t, hidden by solvent peak, 2H), 1.56 (m, J = 7.2, 7.6 Hz, 2H), 0.86 (t, J = 7.6 Hz, 3H).

3-Benzyl-4-(3-methoxyphenyl)-5-(tetrahydrofuran-2-ylmethylsulfanyl)-4*H*-[1,2,4]triazole (35): yield 88%; *m/z* $[M + H]^+$ 382; 98% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.40 (dd, J = 8 Hz, 1H), 7.20−7.18 (dd, J = 8 Hz, 2H), 7.10 (dd, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 2H), 6.76 (m, J = 8 Hz, 3H), 4.02 (m, 1H), 3.99 (s, 2H), 3.72 (s, 3H), 3.71 (m, 2H), 3.32−3.23 (t, hidden by solvent peak, 2H), 1.85−1.80 (m, 2H), 1.70−1.65 (m, 2H).

3-Benzyl-4-(3-methoxyphenyl)-5-(2-methylallylsulfanyl)-4*H*-[1,2,4]triazole (36): yield 81%; *m/z* $[M + H]^+$ 352; 85% pure LC/MS; ^{1}H NMR ($CDCl_3$/DMSO) δ 7.42 (dd, J = 8.4 Hz, 1H), 7.19 (m, J = 7.2 Hz, 2H), 7.08 (dd, J = 8.4 Hz, 1H), 6.95 (t, J = 8.4 Hz, 2H), 6.80−6.73 (m, J = 8.4 Hz, 3H), 4.82 (d, J = 20.4 Hz, 2H), 3.99 (s, 2H), 3.71 (s, 3H), 3.67 (s, 2H), 1.79 (s, 3H).

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