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Synthesis and Evaluation of the Performance of a Small Molecule Library Based on Diverse Tropane-Related Scaffolds

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Abstract

A unified synthetic approach was developed that enabled the synthesis of diverse tropane-related scaffolds. The key intermediates that were exploited were cycloadducts formed by reaction between 3-hydroxy-pyridinium salts and vinyl sulfones or sulfonamides. The diverse tropane-related scaffolds were formed by addition of substituents to, cyclisation reactions of, and fusion of additional ring(s) to the key bicyclic intermediates. A set of 53 screening compounds was designed, synthesised and evaluated in order to determine the biological relevance of the scaffolds accessible using the synthetic approach. Two inhibitors of Hedgehog signalling, and four compounds with weak activity against the parasite *P. falciparum,* were discovered. Three of the active compounds may be considered to be indotropane or pyrrotropane pseudo natural products in which a tropane is fused with a fragment from another natural product class. It was concluded that the unified synthetic approach had yielded diverse scaffolds suitable for the design of performance-diverse screening libraries.

Keywords

molecular diversity; molecular scaffolds; alkaloids; Hedgehog signalling; antimalarials

Introduction

Natural products continue to provide rich inspiration in medicinal chemistry and chemical biology. Natural products have played a crucial role in shaping early-stage drug discovery: 6% of the drugs approved for clinical use between 1981 and 2014 were unaltered natural products, and 26% were natural product derivatives.[1] Furthermore, in biology-oriented synthesis, natural product scaffolds are used to guide the design of productive screening libraries.[2a] Screening libraries can provide useful starting points for the discovery of both drugs and chemical probes, and diversity-oriented synthetic approaches have been developed to increase both the chemical functional diversity that may be explored.[2b-d]

The tropane alkaloids are structurally diverse, and display a broad range of biological functions (Figure 1).[3] Within this class of alkaloids, the [3.2.1]bicyclic tropane core may be substituted at a wide range of positions (as in ecgonine and catuabine A), and can also be fused with additional rings (as in alstoniaphylline B and 2,3-dihydrodarlingine). The tropane core is also in clinically-approved drugs including maraviroc,[4] an HIV-1 entry inhibitor, and atropine, a drug that used to treat bradycardia. The tropane alkaloids have also provided wider inspiration in medicinal chemistry, for example in the discovery of dopamine reuptake inhibitors,[5] muscarinic acetylcholine receptor antagonists[6] and monoamine uptake inhibitors[7] (e.g. **1**). Recently, tropanes have inspired the design of pseudo natural product scaffolds in which the bicyclic is fused with other natural product-inspired ring systems: for example indotropanes[8] (fused with an indole) and pyrrotropanes[9] (fused with a pyrrolidine). The indotropane myokinasib, **2**, is a myosin light chain kinase 1 inhibitor,[8a] whilst **3** is an inhibitor of Hedgehog signalling.[8b]

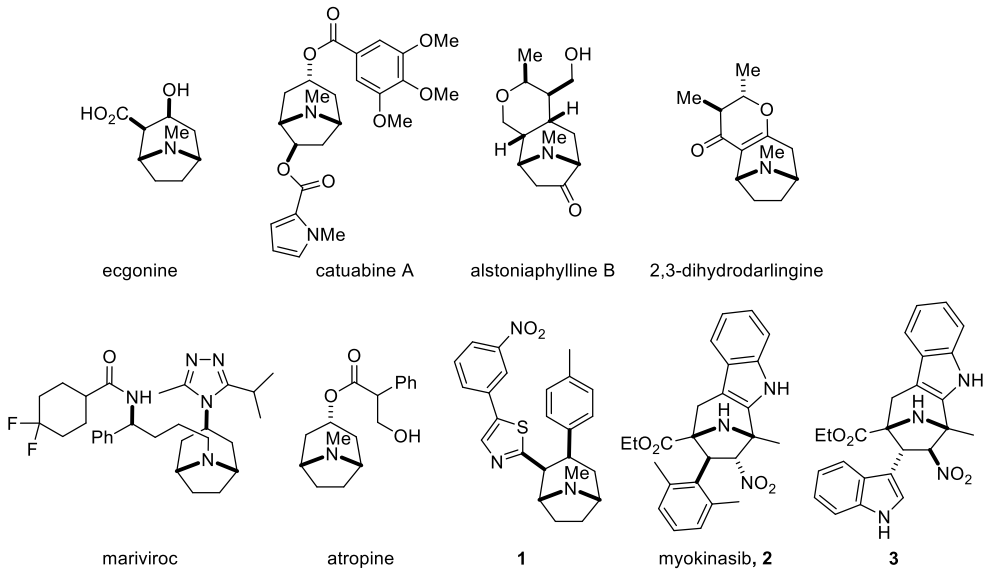
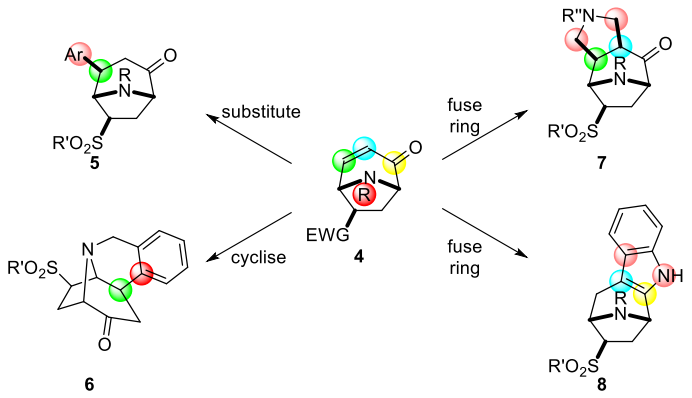


Figure 1: Examples of tropane alkaloids (top) and tropane-related compounds (bottom)

We have developed a unified synthesis of diverse tropane-related scaffolds in which the bicyclic cycloadducts **4** were exploited as key intermediates (Scheme 1).[10] It was envisaged that the functionality in the cycloadducts **4** would enable the addition of substituents to several positions of the tropane core (e.g. to give **5**). Furthermore, the synthesis of more complex tropane-related scaffolds would be possible, either by cyclisation of the cycloadducts **4** (e.g. to give the scaffold **6**) or by fusion of additional ring(s) (e.g. to give the scaffolds **7** or **8**). It was noted that some of the resulting structures may be considered to be pseudo natural product scaffolds in which the tropane core has been fused with other natural product fragments: for example indotropanes (e.g. **8**), tetrahydroquinotropanes (e.g. **6**) and pyrrotropanes (e.g. **7**). In this paper, we describe the development of the unified synthesis, and the design and synthesis of a set of diverse screening compounds based on many of the resulting scaffolds. In addition, we demonstrated the biological relevance of some of the approach through the discovery of both inhibitors of Hedgehog signalling and compounds with activity against *P. falciparum*.

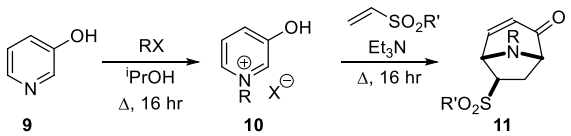


Scheme 1: Overview of the envisaged unified synthetic approach

Results and Discussion

Synthesis of bicyclic intermediates

Initially, we investigated the synthesis of the key bicyclic intermediates (Scheme 2 and Table 1). The 3-hydroxy-pyridinium salts **10** were prepared in near-quantitative yield by alkylation of 3-hydroxy pyridine, and were used without further purification. The 3-hydroxy pyridinium salts **10** and appropriate dipolarophiles were treated with triethylamine, and the corresponding cycloadducts were obtained after reaction at elevated temperature.[11] The reactions proceeded with high regio- and stereoselectivity with a vinyl sulfone or a vinyl sulfonamide as dipolarophile; in contrast, our and other[11] studies showed that the cycloaddition reactions were poorly selective with acrylonitrile or acrylate esters as the dipolarophile. The stereochemical outcome of the cycloadditions was consistent with previous studies,[11] and the relative configurations of derivatives of **11b**, **11c** and **11f** were determined by X-ray crystallography (*vide infra*). Although the yields of the cycloadducts were generally good, lower yields were often obtained with the methylated 3-hydroxy pyridinium salt **10b** which was, nevertheless, consumed during the reactions. It was hypothesised that the iodide counterion dealkylated **10b** under the reaction conditions and, indeed, the yield of **11c** was improved from 20% to 67% when Ag_2O was used as a base that could also remove iodide from solution.



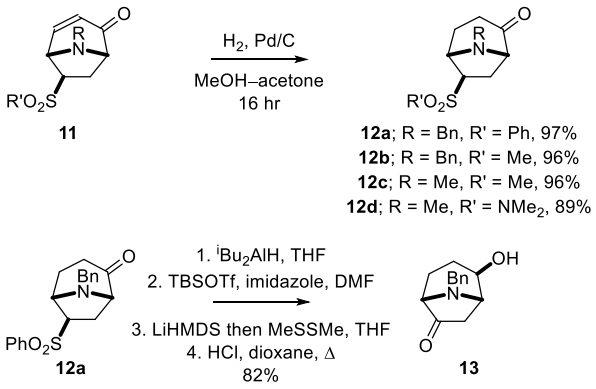
Scheme 2: Synthesis of bicyclic intermediates (see Table 1)

Table 1: Synthesis of bicyclic intermediates (see Scheme 2)

3-Hydroxy pyridinium salt formation				**Bicyclic intermediate formation**		
R	X	Solvent	**Product** (Yield)	**R**	**R'**	**Product** (Yield)
Bn	Br	^{i}PrOH	**10a** (99%)	Bn	Ph	**11a** (70%)
				Bn	Me	**11b** (57%)
Me	I	^{i}PrOH	**10b** (99%)	Me	Me	**11c** (67%)[a]
				Me	NMe_2	**11d** (54%)
				Me	Ph	**11e** (20%)
p-$FC_6H_4CH_2$-	Br	THF	**10c** (99%)	*p*-$FC_6H_4CH_2$-	Me	**11f** (50%)
o-$BrC_6H_4CH_2$-	Br	THF	**10d** (99%)	*o*-$BrC_6H_4CH_2$-	Ph	**11g** (41%)
o-Br-*p*-$FC_6H_3CH_2$-	Br	THF	**10e** (99%)	*o*-Br-*p*-$FC_6H_3CH_2$-	Me	**11h** (89%)

[a]Ag_2O was used as base; 20% yield with Et_3N as base.

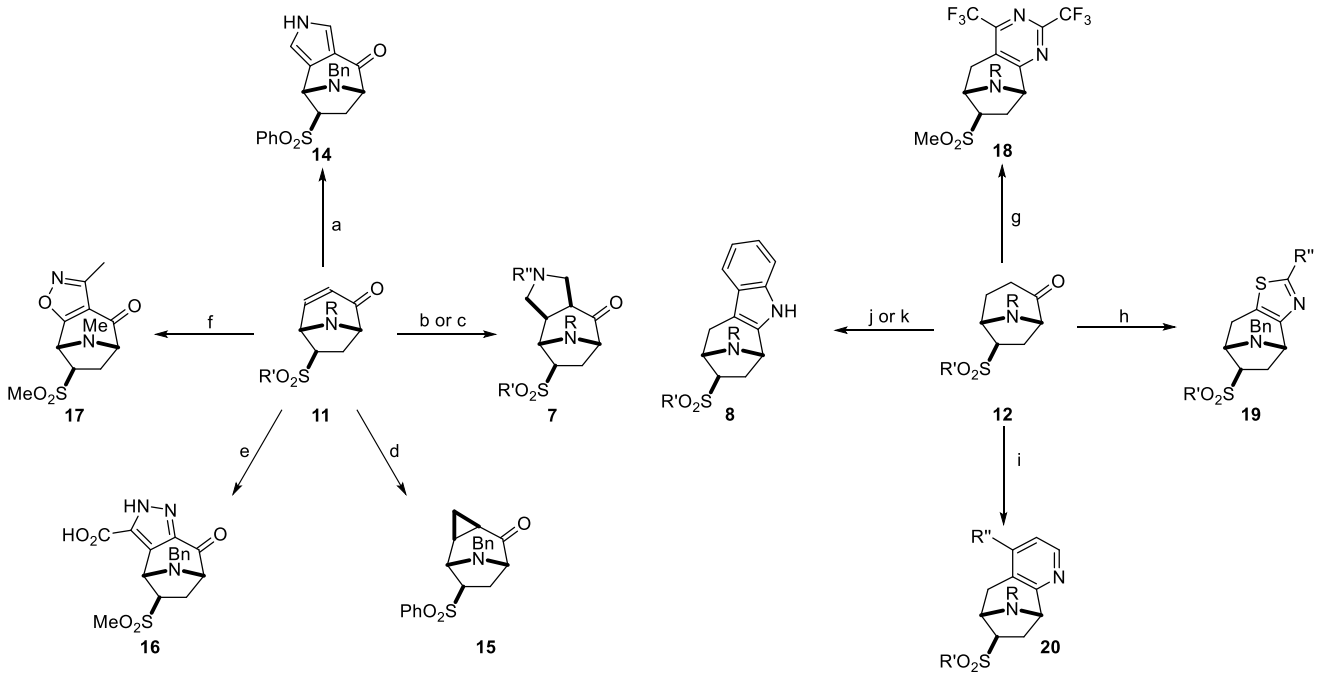
Functional group manipulation of the bicyclic scaffolds **11** was undertaken to enable subsequent scaffold syntheses (Scheme 3). For example, hydrogenation of the enones **11** proceeded in high yield to give the corresponding bicyclic saturated ketones **12**. Furthermore, reduction of **12a** with $^{i}Bu_2AlH$ gave the corresponding alcohol with >98:<2 diastereoselectivity. After TBS protection, the resulting sulfone was treated with LiHMDS and then MeSSMe; subsequent treatment with HCl resulted in hydrolysis of both the α-methylsulfanyl sulfone and the silyl ether to give the ketone **13** in 82% yield over 4 steps.[12]



Scheme 3: Functional group manipulation of bicyclic intermediates

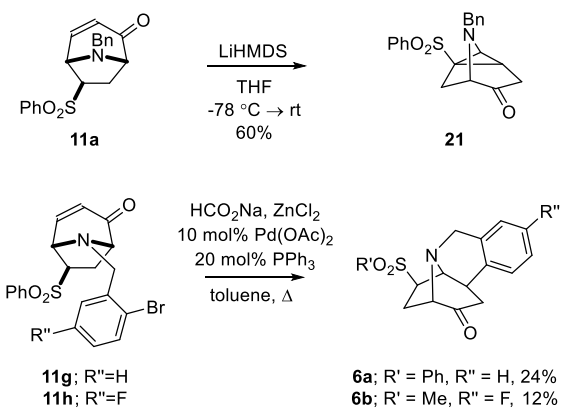
Synthesis of diverse tropane-related scaffolds

A wide range of scaffolds was prepared in which additional ring(s) were fused onto the tropane core (Scheme 4). Treatment of the enone **11a** with toluenesulfonylmethyl isocyanide[13] and potassium *tert*-butoxide gave the corresponding pyrrole **14** in 85% yield. Highly diastereoselective fusion of an *N*-benzyl pyrrolidine ring[14] was possible by treatment of enones **11b**, **11c**, **11e** and **11f** with $Me_3SiCH_2NBnCH_2OMe$ and lithium fluoride in acetonitrile at room temperature (→ **7a-d**, see legend for details).[14a] The relative configuration of a derivative of **7d** was determined by X-ray crystallography (*vide infra*). Alternatively, reaction of the enone **11a** with *N*-methyl glycine and paraformaldehyde[14b] in refluxing toluene resulted in fusion of an *N*-methyl pyrrolidine ring to give **7e** in 77% yield and with high diastereoselectivity. The cyclopropane **15** was prepared in good yield and with >98:<2 diastereoselectivity by treatment of **11a** with dimethyloxosulfonium methylide; the configuration of **15** was determined by correlation with predicted coupling constants for the alternative diastereomers (Supporting Information).[15] Treatment of the enone **11b** with ethyl diazoacetate,[16] followed by hydrolysis with aqueous sodium hydroxide, gave, presumably after aerobic oxidation, the pyrazole **16** in low yield. Finally, reaction of the enone **11c** with an *in situ* generated nitrile oxide[17] could be followed by DDQ oxidation to give the isoxazole **17**.



Scheme 4: Scaffold synthesis by ring fusion onto bicyclic intermediates. Conditions: (a) $TsCH_2NC$, ^tBuOK, THF, 0 °C → rt, 85%; (b) $Me_3SiCH_2NBnCH_2OMe$, LiF, MeCN: **7a** (R=Me, R'=Ph, R''=Bn), 67% (from **11e**); **7b** (R=Me, R'=Me, R''=Bn), 50% (from **11c**); **7c** (R=Bn, R'=Me, R''=Bn), 57% (from **11b**); **7d** (R=*p*-$FC_6H_4CH_2$-, R'=Me, R''=Bn), 88% (from **11f**); (c) $MeNHCH_2CO_2H$, paraformaldehyde, toluene, Δ: **7e** (R=Bn, R'=Ph, R''=Me), 77% (from **11a**); (d) Me_3SO I, NaH, THF, 40%; (e) ethyl diazoacetate, THF then NaOH, H_2O–MeOH, 14%; (f) $EtNO_2$, PhNCO, THF–Et_2O, 28% then DDQ, toluene, Δ, 16%; (g) 2,4,6-tri(trifluoromethyl)-1,3,5-triazine, 10 mol% TFA, EtOH, 80 °C: **18a** (R=Bn), 32% (from **12b**); **18b** (R=Me), 54% (from **12c**); (h) NCS, 30 mol% proline, CH_2Cl_2 then R''$CSNH_2$, DMF: **19a** (R'=R''=Me), 3% over 2 steps (from **12b**); **19b** (R'=R''=Ph), 30% over 2 steps (from **12a**); (i) R'$CCCH_2NH_2$, 2.5 mol% $NaAuCl_4 \bullet 2H_2O$, EtOH, 80 °C: **20a** (R=Bn, R'=Me, R''=H), 63% (from **12b**); **20b** (R=Me, R'=Me, R''=H), 43% (from **12b**); **20c** (R=Me, R'=NMe_2, R''=H), 40% (from **12d**); **20d** (R=Me, R'=Me, R''=Ph), 20% (from **12c**); (j) *o*-$IC_6H_4NH_2$, 10 mol% $Pd(OAc)_2$, DABCO, DMF: **8a** (R=Bn, R'=Ph), 40% (from **12a**); **8b** (R=Me, R'=NMe_2), 29% (from **12d**); **8c** (R=Bn, R'=Me), 20% (from **12b**); **8d** (R=Me, R'=Me), 17% (from **12c**); (k) $PhNHNH_2$, AcOH, Δ: **8a** (R=Bn, R'=Ph), 40% (from **12a**).

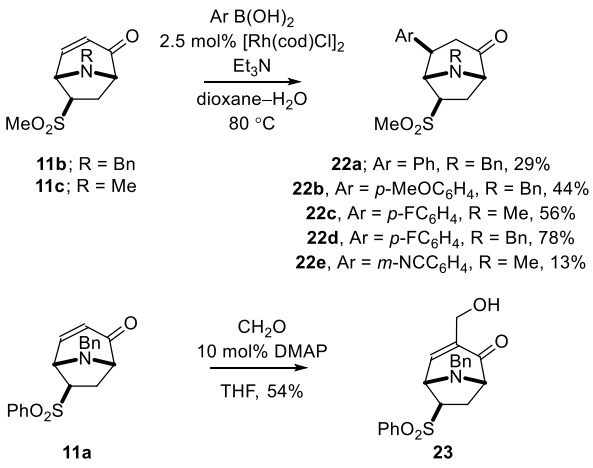
The position of ring fusion to the tropane core could be varied by exploiting the saturated ketones **12** in place of the enones **11** (Scheme 4). Accordingly, treatment of **12b** and **12c** with 2,4,6-tri(trifluoromethyl)-1,3,5-triazine[18] and 10 mol% trifluoroacetic acid in refluxing ethanol gave the pyrimidines **18a** and **18b** in 32% and 54% yield respectively. Alternatively, α-chlorination of the ketones **12a** and **12b**,[19] followed by reaction with thioacetamide or thiobenzamide,[20] gave the thiazoles **19**. Fusion of a pyridine ring was possible by treatment of the ketones **12** and an appropriate propargylamine with 2.5 mol% $NaAuCl_4$ (→ **20**).[21] Finally, either Fischer indole synthesis[22] or Pd-catalysed indole formation[23] enabled conversion of the ketones **12** into the corresponding indotropanes **8**.



Scheme 5: Scaffold synthesis by cyclisation of bicyclic intermediates.

Two complementary cyclisation reactions enabled conversion of the enones **11** into more complex scaffolds (Scheme 5). Treatment of **11a** with MeLi resulted in deprotonation and cyclisation, rather then methyl addition to the ketone, to give the cyclopropane **21** in 20% yield; the yield of the process was improved to 60% with LiHMDS as base in place of MeLi. Finally, reductive Heck cyclisation[24] between the aryl bromide and the enone of **11g** and **11h** gave the tetrahydroquinotropanes **6a** and **6b**.

Substitution of the enones **11** was possible at alternative positions (Scheme 6). Rh-catalysed conjugate addition[25] of aryl-boronic acids to the enones **11b** and **11c** yielded the corresponding aryl-substituted tropanes **22a-e** with high diastereoselectivity. The relative configuration of derivatives of **22c** and **22d** was determined by X-ray crystallography (*vide infra*). In addition, a Bayliss-Hillman reaction of the enone **11a** yielded the hydroxymethyl-substituted enone **23**.



Scheme 6: Exploration of alternative vectors by functionalisation of bicyclic intermediates

The unified approach had enabled the synthesis of sixteen distinct deprotected graph-node-bond level[26] scaffolds in which alpha atoms had been removed. The diversity of these scaffolds may be captured in terms of an hierarchical tree[27] that formalises the relationship between molecular scaffolds (Figure 2). We used the open access-computional tool LLAMA[28] to assess the novelty of the scaffolds with respect to a random 2% of the ZINC database of commercially-available compounds.[29] Only two of the 16 final scaffolds were found as substructures of these compounds: the pyrimidine-containing scaffold and the parent tropane core.

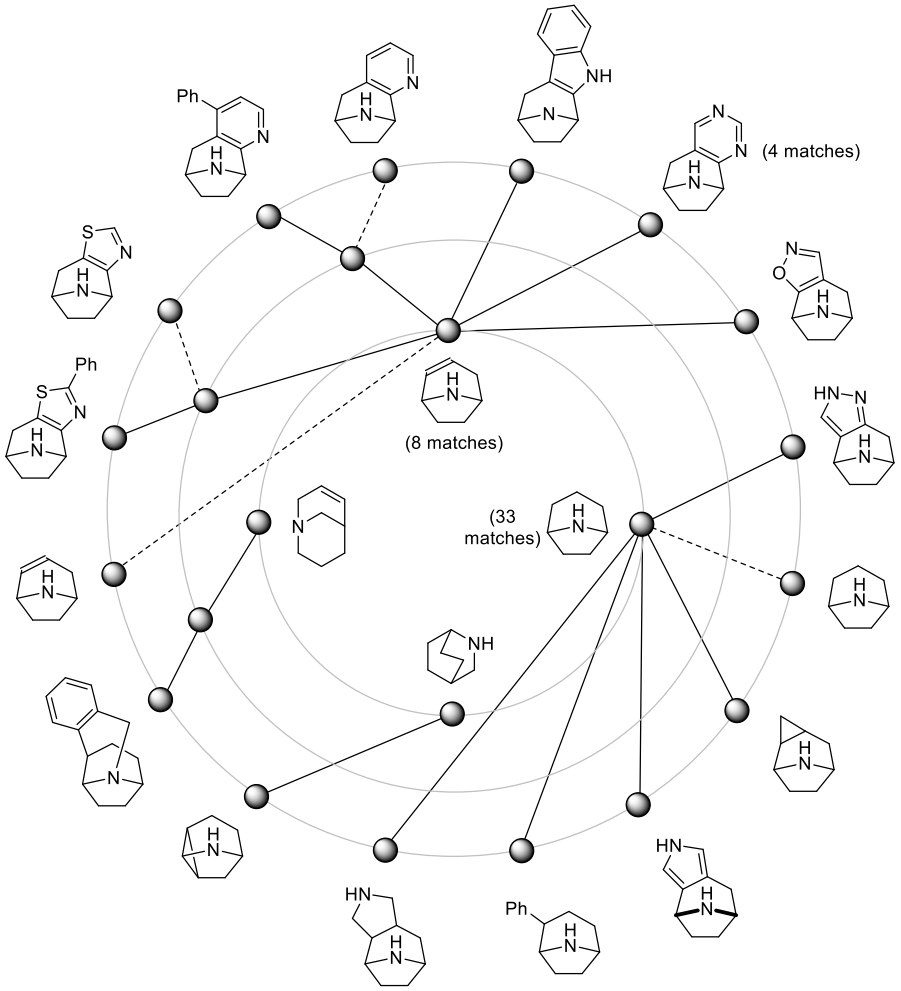
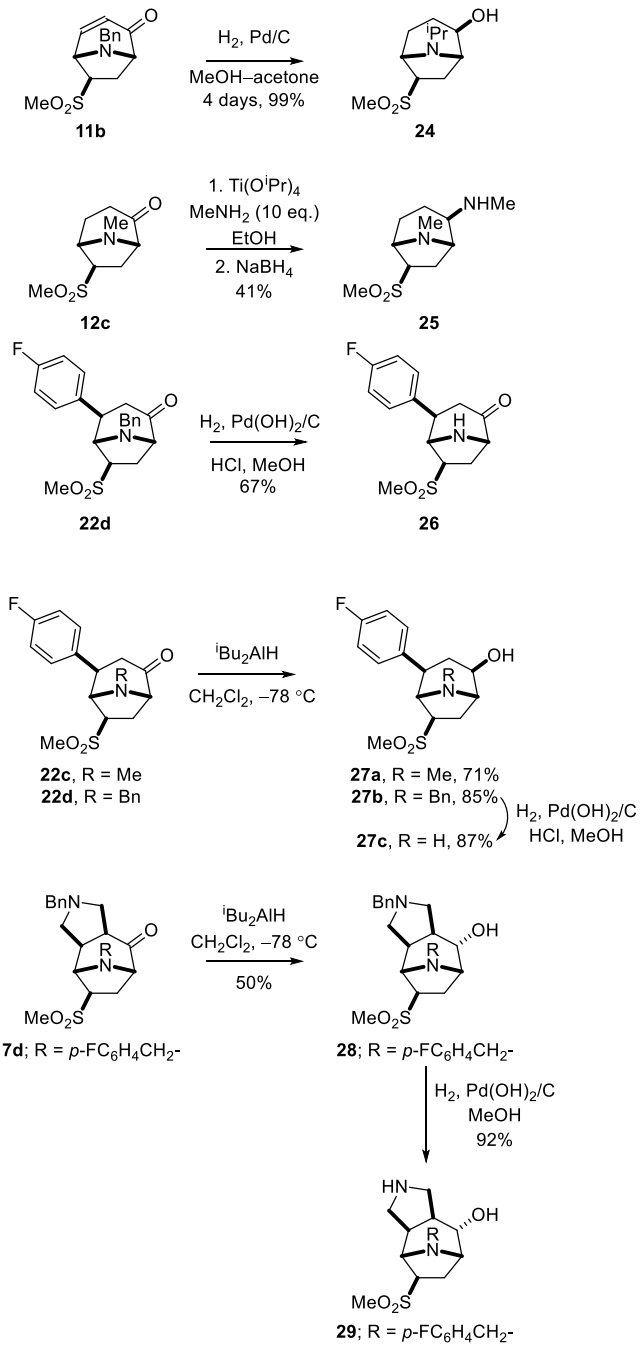


Figure 2: Hierarchical relationship between the tropane-related scaffolds. Scaffolds that were found as substructrues of a random 2% of the ZINC database of commercially-available compounds are noted.

Design, synthesis and evaluation of a small molecule library based on diverse tropane-related scaffolds

A range of building blocks was prepared in which the protecting groups were chosen to enable decoration of the scaffolds at complementary positions (Scheme 7). Hydrogenation of the enone **11b** under forcing conditions in methanol–acetone resulted in debenzylation, alkene and ketone reduction and *iso*-propylation (by reaction with acetone) to give the hydroxyl-substituted tropane **24**. Reductive amination of the ketone **12c**, by treatment with methylamine, $Ti(O^iPr)_4$ and then sodium borohydride gave the secondary amine **25** in 41% and with high diastereoselectivity; the relative configuration of similar reductive amination products was determined by NOESY analysis (Supplementary Information). In a similar vein, reaction of the ketones **22c**, **22d** and **7d** with $^iBu_2AlH$ was moderately diastereoselective (crude dr observed with these substrates: **22c**, 75:25; **22d**, 90:10; **7d**, 75:25) and, after purification, yielded the corresponding alcohols **27a**, **27b** and **28** as single diastereomers. Finally,

hydrogenolysis of **22a**, **27b** and **28** yielded the corresponding debenzylated building blocks **26**, **27c** and **29**. The relative configuration of **27a**, **27b** and the 2-methyl-propionamide of **29** were determined by X-ray crystallography (Supporting Information).[30]



Scheme 7: Synthesis of building blocks for library synthesis

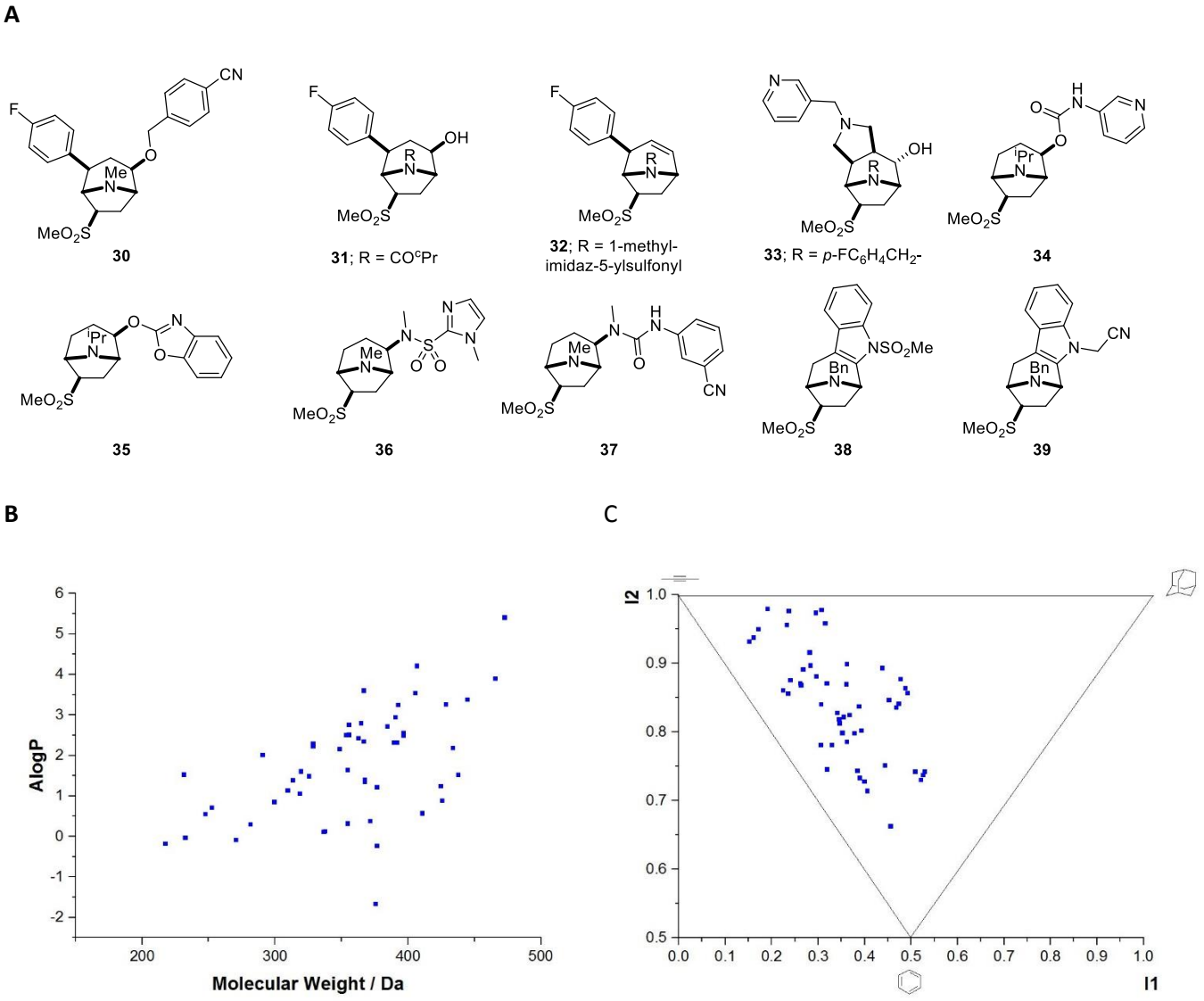


Figure 3: Construction of a set of 53 screening compounds. Panel A: Exemplar screening compounds (see Table 2 for synthesis and Supplementary Information). Panels B and C: Molecular properties (B) and shape diversity (C) of the library (see Supplementary Information). Shape diversity is represented on a principal moments of inertia (PMI) plot in which the vertices correspond to linear (top left), flat (bottom) and spherical (top right) shapes.

A set of 53 screening compounds based on many of the tropane-related scaffolds was designed and prepared. In addition to compounds that had already been prepared (**6a**, **6b**, **8b**, **8c**, **8d**, **12c**, **13**, **14**, **16**, **17**, **18a**, **18b**, **19a**, **19b**, **20a**, **20b**, **20c**, **20d**, **22e**, **24**, **25**, **27a**, **27c** and **29**), additional compounds were also synthesised by derivatisation of building blocks (see Scheme 7) with a single capping group. Final compounds were generally purified by mass-directed HPLC or automated reverse-phase flash column chromatography; purification was often challenging, and low yield of purified products were often obtained using these methods. The synthesis of ten exemplar screening

compounds (see Figure 3, Panel A) is summarised in Table 2 (see also Supplementary Information). The molecular properties (Panel B) and shape diversity (Panel C) of the screening compounds is summarised in Figure 3. The screening compounds generally have drug-like molecular properties, and are more three-dimensional than many screening sets.[31]

Table 2: Synthesis of exemplar screening compounds

Substrate	**Method**	**Product** (Yield)
27c	4-bromomethyl-benzonitrile, NaH, DMF	**30** (12[a])
27c	[c]PrCOCl, pyridine, CH_2Cl_2	**31** (16[a])
27c	1-methylimidazole-2-sulfonyl chloride, pyridine, DMF	**32** (4[a])
29	isonicotinaldehyde, DMF then $NaBH_4$	**33** (41[b])
24	4-methoxyphenylisocyanate, NaH, DMF	**34** (10[b])
24	2-chlorobenzoxazole, NaH, DMF	**35** (7[b])
25	1-methylimidazole-2-sulfonyl chloride, pyridine, DMF	**36** (21[b])
25	3-isocyanatobenzonitrile, $NaHCO_3$, DMF	**37** (35[b])
8c	MsCl, NaH, DMF	**38** (11[b])
8c	$BrCH_2CN$, NaH, DMF	**39** (19[b])

[a]Purification by mass-directed HPLC. [b]Purification by automated reverse-phase flash column chromatography.

The 53 final compounds were screened in two phenotypic assays that were selected as representative applications of the library. It was intended that these assays would enable a preliminary assessment of the biological relevance of the scaffolds accessible using the unified synthetic approach. An osteoblast differentiation assay[32] was used to screen the compounds, initially at 10 μM, for inhibition of Hedgehog signalling. The dose-dependent activity of hits, identified on the basis of at least 50% inhibition of signallig and <20% impact on cell viability, was determined. In addition, a screen against a NF54 (chloroquine-susceptible) *P. falciparum* strain was performed in dose-response mode in which lactate dehydrogenase activity served as a marker for parasite viability.[33] The dose-dependent activity of the active compounds from both assays is shown in Figure 4. Two inhibitors of Hedgehog signalling were discovered (**38** and **39**; Panel A), both of which were based on a tetracyclic indotropane scaffold that is a substructure of some known[8b] inhibitors of this pathway (such as **3**, Figure 1). Four

compounds with weak antiplasmodium activity were also identified (**16**, **20**, **40** and **41**; Panel B); these compounds were based on four distinct tropane-related scaffolds that had been prepared. We note that three of the active compounds may be considered to be pseudo natural products in which a tropane is fused with a fragment from another natural product class: **38** and **39** are indotropanes and **41** is a pyrrolotropane.[9]

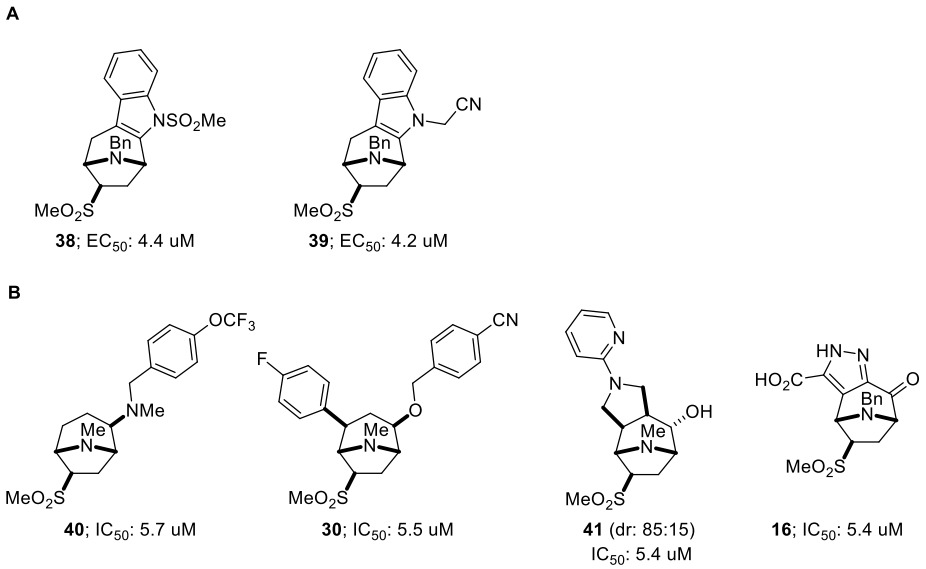


Figure 4: Structures of bioactive ligands discovered. Panel A: Inhibitors of Hedgehog signalling. Panel B: Inhibitors of *P. falciparum* survival. Compound **41** was tested as a 85:15 mixture of diastereomers.

Conclusion

A unified synthetic approach was developed that enabled the synthesis of diverse tropane-related scaffolds. The bicyclic cycloadducts **11** were exploited as key intermediates which were converted into diverse scaffolds by the addition of substituents, cyclisation reactions, and the fusion of additional ring(s). In total, the approach enabled the synthesis of sixteen distinct scaffolds, only two of which were found in a substructure search of commercially-available compounds. The biological relevance of the scaffolds that were accessible using the approach was determined by design, synthesis and evaluation of 53 screening compounds. The set of screening compounds was screened, enabling discovery of two inhibitors of Hedgehog signalling and four compounds with activity against *P. falciparum*. Three of these compounds may be considered to be indotropane or pyrrotropane pseudo natural products in which a tropane is fused with a fragment from another natural product class. We

conclude that unified approaches for the synthesis of diverse natural product-inspired scaffolds can underpin the design of performance-diverse screening libraries.

Acknowledgments

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