# A Tryptoline Ring Distortion Strategy Leads to Complex and Diverse Biologically Active Molecules from the Indole Alkaloid Yohimbine

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## Abstract

High-throughput screening (HTS) is the primary driver to current drug discovery efforts. New therapeutic agents that enter the market are a direct reflection of the structurally simple compounds that make up screening libraries. Unlike medically relevant natural products (e.g., morphine), small molecules currently being screened have low fraction $sp^3$ character and few, if any, stereogenic centers. Although simple compounds have been useful in drugging certain biological targets (e.g., protein kinases), more sophisticated targets (e.g., transcription factors) have largely evaded the discovery of new clinical agents from screening collections. Here, we describe a tryptoline ring distortion strategy that enabled the rapid synthesis of 70 complex and diverse compounds from yohimbine **1**, an indole alkaloid. The compounds that were synthesized had architecturally complex and unique scaffolds, unlike **1** and other scaffolds. These compounds were subjected to phenotypic screens and reporter gene assays leading to the identification of new compounds that possess various biological activities, including: antiproliferative activities against cancer cells with functional hypoxia inducible factors, nitric oxide inhibition, inhibition and activation of the antioxidant response element (ARE). This tryptoline ring distortion strategy can begin to address diversity problems in our screening libraries while occupying biologically relevant chemical space in areas critical to human health.

## Graphical abstract

Rapid Synthesis of 70 Complex and Diverse Small Molecules as a Driver to Biological Discovery
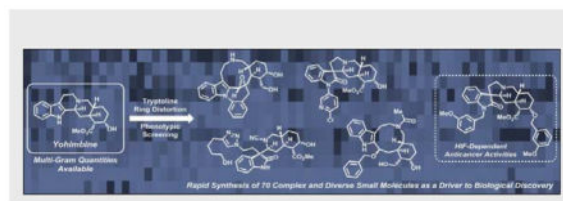
## Keywords

drug discovery; tryptoline; ring distortion; yohimbine; biological screening

## Introduction

Through the 1980's, natural products were the primary source of new drug molecules as efforts to discover new biologically active compounds involved screening collections of natural products or crude extracts.[1] These were highly fruitful expeditions that gave us bioactive entities, such as morphine, vancomycin and taxol, which all possess exquisite biological activities due to their complex molecular structures interacting with their corresponding biological target in a highly specific and selective fashion. Due to advances in molecular biology, solid-phase synthesis and screening technologies, the 1990's led to a paradigm shift from screening natural products/extracts in whole-cell (phenotype) screens to large collections of relatively simple organic compounds (containing low $sp^3$-character and essentially no stereochemistry) and target-based, high throughput screens (HTS).[2,3]

HTS has become the primary driver in drug discovery and has led to several FDA-approved drugs, including: gefitinib, erlotinib, sorafenib, tipranavir, tolvaptan and lapatinib.[2] Despite success in drugging certain protein targets (tyrosine kinases), current screening libraries have been ineffective at targeting more sophisticated biological targets (i.e., protein-protein interactions[4–6], transcription factors[7,8]) and disease areas (i.e., antibiotic-resistant bacteria[3]). The inability of current screening libraries to produce compounds that effectively drug "undruggable" biological targets are attributed to an underrepresentation of chemical diversity, or chemical space.[3,9–11] As such, complex and diverse small molecules are of significant interest to drug discovery.

Several elegant synthesis strategies have been developed to address chemical diversity deficiencies through the rapid synthesis of complex molecules for biological screening; however, the two most well-known approaches include: diversity-oriented synthesis[9,12–17] (DOS; pioneered by Schreiber and co-workers) and biology-oriented synthesis[18–23] (BIOS; led by Waldmann and co-workers). Additionally, alternative and elegant syntheses of natural product-inspired scaffolds has been an area of significant interest in recent years.[24–26] These strategies are aimed at capturing various structural features of natural products (i.e., fused ring systems, stereochemical complexity) into small molecules that can be rapidly accessed for biological screening. DOS and BIOS have led to several interesting biological discoveries in diverse disease areas and are promising approaches to the identification of therapeutic leads and probe molecules to interrogate biological systems.[20,22,23,27–29]

An alternative "ring distortion" approach utilizes available natural products containing a complex and fused ring system as synthetic starting points. Through rapid synthetic sequences from the selected natural product, the strategic goal is to dramatically alter the complex ring system inherent to the natural product thus generating complex small molecules with unique and diverse molecular architectures.[30] Ring distortion involves the altering of complex ring systems through various chemical reactions that enable ring cleavage, expansion, rearrangement and fusion.[30–32] The Hergenrother lab has carried out ring distortion campaigns on gibberellic acid[30], adrenosterone[30], quinine[30], abietic acid[31] and pleuromutilin.[32] These have been largely successful due to the utility of strategically useful ketone- and alkene-based chemistries in addition to complex molecular frameworks that enable dramatic ring rearrangement reactions for ring distortion.

Indole-containing compounds span an array of chemical space from complex natural products to very simple compounds (Fig 1A, indoles **1–9**). Interestingly, simple and complex indole-containing compounds demonstrate diverse biological activities due to the numerous biological targets that bind various indoles, making the indole nucleus a privileged scaffold that occupies an interesting and biologically relevant chemical space. Yohimbine **1** is a complex indole alkaloid isolated from the bark of Pausinystalia trees and the Rauwolfia root that acts as an $\alpha_2$-adrenergic receptor antagonist.[33] This alkaloid is highly abundant and sold over-the-counter for its fat-burning/stimulatory and aphrodisiac properties. We became interested in **1** as a starting point for ring distortion due to its highly complex ring system fused to an indole nucleus. Multiple synthetic reactions of **1** as a starting material have been reported in the literature, including: oxidation of the secondary alcohol[34], allylation of the 3-position of the indole nucleus[35], alkylation of the indole nitrogen[36], hydroxylation of the indole nitrogen[37,38], reduction of the 2,3-positions of the indole heterocycle[37,38], and ethylene glycol protection of the 2,3-positions of the indole nucleus.[39] Our ring distortion strategy involved two known transfromations, including: cyanogen bromide ring cleavage with alcohols[40] and transformation of **1** into a spirooxindole-containing scaffold.[41] Yohimbine **1** provides an outstanding platform to develop an innovative ring distortion strategy involving the basic reactivity of the indole heterocycle to rapidly generate complex and diverse small molecules for biological screening in diverse disease areas (i.e., cancer, inflammation, drug-resistant bacteria).

## Results and Discussion

### Tryptoline-Based Ring Distortion Strategy

We devised a ring distortion strategy based on two structural features connected through the tryptoline **10** sub-structure of **1**, which include: 1.) the centrally positioned basic nitrogen with three unequivocal C-N bonds (bonds B, C and D; Fig 1B), ideal for dramatic and diverse ring cleavage reactions to afford **11–13** and 2.) oxidative rearrangement of the 2,3-disubstituted indole nucleus to give ring-rearranged product **Y7b** (bond A; Fig 1B). Our goals were to develop short synthetic sequences that involve ring distortion reactions directly from **1** to enable optimal choreographing of ring cleavage, scrambling, fusion or rearrangement reactions in tandem with subsequent diversification reactions (i.e., click chemistry). This tryptoline ring distortion strategy was developed to generate several

complex and diverse scaffolds totaling 70 small molecules in rapid synthetic sequences from **1** (Fig 1C).

## Ring Distortion of the Indole Alkaloid Yohimbine

Initially, we targeted the C-N bonds of yohimbine's central amine for regioselective ring cleavage reactions. Using cyanogen bromide (BrCN), we were able to activate the basic nitrogen of **1** to give intermediate **14** (Scheme 1), from which we generated numerous diverted ring-distorted compounds. Two of the unequivocal C-N bonds of **1** could be selectively cleaved with cyanogen bromide through careful selection of solvent.

Cyanogen bromide C-N ring cleavage of **1** proceeds through an $S_N2$ pathway in dimethylformamide (DMF; Scheme 1A). The liberated bromide anion generated upon formation of **14** attacks the most accessible "b" carbon adjacent to the activated central nitrogen of **14** in only 3 minutes using microwave irradiation resulting in **Y1a** as the only observed product. We were able to successfully carry this reaction out on a 985 milligram scale (45% yield), which was crucial for subsequent analogue synthesis.

Contrasting to the $S_N2$ pathway, a 3:1 chloroform:alcohol solvent mixture results in an $S_N1$-like pathway in which the alcohol is a nucleophile and attacks the "a" carbon of **14**. This reaction has been previously described[40]; however, we extended this reaction by utilizing diverse alcohol solvent/nucleophiles, which react with intermediates **14** and **15** to yield diastereomeric mixtures of ethers **16** ("$S_N2$ product"; inverted stereochemistry at "a") and **17** ("$S_N1$ product"; retention of stereochemistry at "a"). Diastereomers produced from this reaction can be readily separated via chromatography and tested in biological screens. Interestingly, less sterically encumbered alcohols (i.e., methanol) gave "$S_N2$ products" (i.e., **16**) as the major diastereomer (3.4:1 to 50:1 drs; Scheme 1A), which can be rationalized by considering that **14** and **15** can permit less hindered nucleophiles to undergo "back-side attack" at carbon "a" of structure **14**. Alcohols with more steric bulk (i.e., 2-iodobenzyl alcohol) gave ~1:1 mixtures of diastereomeric products, which can be explained through an $S_N1$-like mechanism involving nucleophilic attack of both faces on resonance-stabilized carbocation **15**. This ring-cleavage reaction proceeded in 14–63% yield (11 examples yielded 19 ethers) and the major diastereomers were isolated on scales between 6.9 and 576 milligrams, which is sufficient for additional ring distortion reactions, analogue synthesis and biological screening.

We took advantage of the lack of diastereocontol of cyanogen bromide/alcohol ring cleavage to generate diverted ring fusion products **Y4a** and **Y5a** (Scheme 1B), which have unique complex molecular architectures. Yohimbine was initially subjected to cyanogen bromide ring cleavage in chloroform:2-iodobenzyl alcohol to give a 1.2:1 diastereomeric mixture of **Y6r** and **Y6s** (47% combined yield). The diastereomeric mixture was readily separated and each diastereomer was taken forward and subjected to copper(I) iodide-catalyzed intramolecular C-N coupling between the aryl iodide and indole nitrogen to give diverted ring fusion products **Y4a** (70%) and **Y5a** (73%) on 163–222 milligram scale.

Indole heterocycles can undergo oxidation with subsequent alkyl migration, translating to a ring rearrangement of **1**. An oxidative rearrangement such as this allows us to take advantage

of the intrinsic reactivity of the indole ring, which was a critical aspect of our tryptoline ring distortion strategy. A three-step, oxidative-rearrangement of yohimbine to afford ring-rearranged spirooxindole **Y7b** (Scheme 1C) was previously reported.[41] Although initial attempts to repeat the literature chlorination reaction with hypochlorite failed in our hands, this was remedied by using *N*-chlorosuccinimide (NCS) to afford clean chlorination at the 3-position of the indole of **1**. This was followed by treatment with sodium methoxide (NaOMe) to induce stereospecific alkyl migration and expulsion of the 3-chloro group. Final treatment with trifluoroacetic acid (TFA) afforded ring-rearranged product **Y7b** (38%/3 steps). We were able to generate 748 milligrams of **Y7b** in one run through this three step route during these investigations without focused scale-up efforts.

We subjected **Y7b** to cyanogen bromide ring cleavage in DMF to afford **Y2a** as a single product in 52% yield (233 milligrams; Scheme 1C; X-ray in Supporting Information). The propensity of bromide to attack the "b" carbon of **Y7b** can be rationalized by an $S_N2$ attack of the least sterically encumbered carbon atom of the respective cyanamide intermediate (not shown). Despite many attempts, ring cleavage at the "D" bond (Fig 1B) of **1** was evaded; however, future developments are aimed to address this to generate interesting structures similar to **13**.

The rapid, tryptoline-based ring distortion pathways developed during these investigations were highly efficient in the generation of several new scaffolds in 1 to 4 steps from **1**. During these investigations, multiple C-N bonds to the central nitrogen atom of **1** were selectively cleaved with cyanogen bromide, an oxidative rearrangement of the indole heterocycle of **1** was utilized and C-N bond coupling reactions were used in ring fusion reactions to generate diverted complex scaffolds. Overall, this tryptoline ring-distortion platform enabled the rapid synthesis of novel complex and diverse chemotypes that are important to biological screening and drug discovery efforts.

## Diversification of Ring Distorted Compounds

Following tryptoline ring distortion of **1**, our goals were to decorate newly synthesized complex and diverse scaffolds using more traditional diversification strategies. This allows for the synthesis of sub-libraries for each scaffold enabling further exploration of chemical space during biological screening endeavors. Diversification of yohimbine-derived architectures found in Scheme 1 was ideal as these complex small molecules are endowed with multiple functional groups serving as potential synthetic handles for library generation.

**Reactions that lead to ring distortion AND chemical diversification (sub-libraries) in the same step are highly useful in this approach**—For example, subjecting **1** to cyanogen bromide and 11 different alcohols (including water; Scheme 1A) led to 19 total ring-cleaved ethers (**Y6a-Y6s**; Scheme 2). The library potential for this reaction was enhanced as two diastereomers are typically produced from this reaction. In 8 of the 11 examples, both diastereomers were isolated (pure) for biological screening and additional synthesis efforts.

Due to the synthetic utility of cyanogen bromide in ring cleavage reactions, multiple ring-cleaved compounds contained primary bromides (**Y1a** and **Y2a**) which were subjected to

sodium azide displacement ($S_N2$) to yield azides **Y1b** and **Y2b**, respectively (Scheme 2). Each azide was then subjected to copper(I)-catalyzed click reactions with a diverse panel of available terminal alkynes to generate two diverse triazole sub-libraries (**Y1c-Y1h**, 6 examples, 61% average yield; **Y2c-Y2p**, 14 examples, 69% average yield).

We found ring-rearranged **Y7b** to be very useful in diverted library synthesis due to the amide and hydroxyl functional groups readily available as synthetic handles. Ten mono- or dialkylated products of **Y7b** were synthesized with available alkyl halides (**Y7c-Y7l**, 47% average yield; Scheme 2). **Y7b** was also diversified using copper(I)-catalyzed C-N coupling between the amide nitrogen and nine diverse (hetero)aryl iodides (29% average yield).

Other synthetic modifications were made to yohimbine-derived small molecules, including: 1) lithium aluminum hydride reductions of cyanamide/ester functional groups and 2) acylation (Supporting Information). These efforts resulted in 70 complex and diverse compounds synthesized from yohimbine using rapid and diverted synthetic pathways. During these investigations, we were able to synthesize each of the analogues in these sub-libraries on a 6.0 to 576 milligram scale, which is sufficient for extensive biological investigations.

## Biological Investigations of Yohimbine-Derived Small Molecules

We screened our yohimbine ring distortion library in several phenotypic and focused pathway-specific screens related to cancer and inflammation as well as pathogenic bacteria (Fig 2A). Specifically, we aimed to identify selective antiproliferative agents that preferentially act on cancer cells with functional hypoxia-inducible factors (HIF) pathways. HIF transcription factor mediated signaling is known to be activated in cancer and linked to angiogenesis, cell growth, survival and metastasis. We employed isogenic HCT116 colorectal cancer cell lines, including parental HCT116 and HCT116 double knockout cells lacking HIF-1α and HIF-2α,[42,43] and screened our library for differential antiproliferative activity. Of the 70 compounds tested, **Y7g** stood out as the most selective antiproliferative agent upon dose-response analysis (Fig 2B), suggesting that this compound could be a starting point for the development of selective and more potent HIF inhibitors. Chronic inflammation is a known factor in the etiology of colorectal cancer and, intriguingly, the same compound (**Y7g**) also showed the most selective anti-inflammatory activity in RAW264.7 macrophage cells based on the inhibition of nitric oxide (NO) production (Fig 2C). Cell viability was almost unaffected in this cell type, further supporting the cancer cell selectivity of **Y7g**.

We then assessed the potential of the library compounds to modulate the activity of another key transcription factor, NF-E2-related factor 2 (Nrf2), which acts on the antioxidant response element (ARE) in the promoter region upstream of antioxidant and phase II detoxification enzymes. Activators of the Nrf2-ARE pathway have potential as cancer preventive agents because of their ability to increase antioxidant status of the cell and protect from oxidative damage that could lead to cancer. Inhibitors in turn may increase the susceptibility of cancer cells to chemotherapeutic agents and overcome drug resistance since Nrf2 is commonly activated in cancer.[44] To screen for Nrf2 inhibitors, we used MDA-MB-231 breast cancer cells (a model for invasive, triple negative breast cancer) stably

transfected with the ARE-luciferase reporter, where the promoter region is derived from the human NQO1 gene.[45] As a control, we monitored cell viability to ensure the identification of false positives in the reporter gene assay that are a result of concomitant reduced cell viability. We selected **Y3e**, **Y6q** and **Y1f** for validation by RT-qPCR, assessing the effects of the compounds on the transcription of the endogenous Nrf2 target gene, *NQO1*, in comparison with brusatol.[46] All three compounds downregulated *NQO1* transcription (Fig 2D).

To identify activators of Nrf2 we transiently transfected LNCaP androgen-sensitive prostate cancer cells with ARE-luciferase reporter based on the human *NQO1* promoter[47–49] and then challenged them with our yohimbine library. As a control, we monitored LNCaP viability in parallel (Fig 2E). While many compounds activated the ARE at 100 μM potentially as a stress response, **Y5b** and **Y6u** were also active at lower concentrations when we validated the hits by RT-qPCR for levels of endogenous *NQO1*. These compounds were only slightly less potent than the positive control, sulforaphane.

We also screened our yohimbine library against *Staphylococcus aureus* (Gram-positive pathogen) and *Acinetobacter baumannii* (Gram-negative); however, only a few compounds demonstrated weak antibacterial activities (i.e., partial growth inhibition) against *A. baumannii* at 200 μM. We did find the antibacterial screen insightful to cross-reference activity profiles of validated hit compounds with selective antiproliferative, NO inhibition and Nrf2-ARE modulation. Of the six validated hit compounds identified during these biological investigations (**Y7g**, **Y6q**, **Y3e**, **Y1f**, **Y5b**, **Y6u**; Figure 2), only **Y1f** and **Y6q** demonstrated slight (~20%) growth inhibition activities at 200 μM against *S. aureus*. Interestingly, we note that **1** does not possess any of these activities inherently, illustrating the potential for yohimbine, and other natural products, to reach beyond their own biological capabilities using this ring distortion approach. Overall, yohimbine ring-distorted small molecules cover a biologically relevant chemical space as evident by the diverse array of active compounds we identified in a relatively small library of 70 compounds.

Indole alkaloids possess an array of complex molecular architectures that is able to produce diverse biological activities as this class of natural products has intrigued scientists for decades.[50–54] Total synthesis efforts date back to Woodward's elegant construction of (±)-reserpine[52] reported in 1956 and continue to inspire the development of new synthetic methods and approaches[53] today, including Jacobsen's 2013 total synthesis of (+)-reserpine.[54]

As alternative synthesis approaches have emerged to drive biological discoveries, indoles have remained a considerable interest as unnatural indole small molecules have demonstrated impressive biological activities in diverse disease areas of importance to human health. Synthetic efforts have led to the discovery of indoline compounds capable of resensitizing methicillin-resistant *Staphylococcus aureus* to methicillin[55,56] while indole-inspired BIOS has led to the identification of inhibitors of protein phosphatases, which are important drug targets for diabetes and cancer.[19] BIOS efforts have also led to the discovery of spirooxindole small molecules that influence neuronal network formation and demonstrate neurite outgrowth-promoting activities.[22]

Here, we utilized the complex indole alkaloid, yohimbine **1**, as a starting point for diverted ring distortion by combining the inherent reactivity of the indole nucleus with the tryptoline scaffold as a complementary approach to DOS and BIOS, termed "Complexity-to-Diversity" (CtD). New ring-distorted compounds from **1** were advanced through further derivatization and subjected to initial biological screens leading to the discovery of **Y7g** which demonstrated dual HIF-dependent anticancer and anti-inflammatory activities while five additional ring distorted compounds (**Y6q**, **Y3e**, **Y1f**, **Y5b**, **Y6u**; Figure 2) were found to selectively modulate the ARE pathway in cancer cell lines.

We compared the yohimbine ring distortion library to a ChemBridge (commercial) Library[31] and the 100 top-selling, FDA-approved drugs from 2013 by analyzing the number of stereocenters per compound and fraction $sp^3$ ($Fsp^3$) character for compounds in each library (Fig 3). Each compound from our yohimbine-derived library averages $5.54 \pm 0.53$ stereocenters, which is considerably higher than the FDA-approved drugs ($2.58 \pm 2.61$ stereocenters per compound) and the ChemBridge Library (0.24 stereocenters per compound). The $Fsp^3$ character for the yohimbine-derived library is $0.50 \pm 0.08$ which is similar to the FDA-approved drugs ($Fsp^3 = 0.49 \pm 0.21$) and higher than the ChemBridge library ($Fsp^3 = 0.24$).

These combined efforts led to the identification of multiple biologically active, ring-distorted small molecules from **1** demonstrating the potential for this ring distortion approach to discover new biologically active compounds. This complex and diverse library of small molecules occupies biologically relevant chemical space. Future work will include developing improved analogues of the hit compounds identified and validated during these studies.

## Conclusions

In conclusion, we have developed a new tryptoline-based ring distortion strategy that utilized the indole heterocycle of yohimbine to carry out diverse ring cleavage, ring rearrangement and ring fusion reactions enabling the rapid synthesis of multiple scaffolds totaling 70 complex and diverse small molecules. The resulting library was screened for biological activity and several hit compounds were identified in an array of assays, including **Y7b** which demonstrated HIF-dependent anticancer and anti-inflammatory activities. This tryptoline-based ring distortion has clear potential for the discovery of new biologically active small molecules. Hit-to-lead optimization of active compounds identified during these investigations are currently underway and aim to address multiple disease areas critical to human health.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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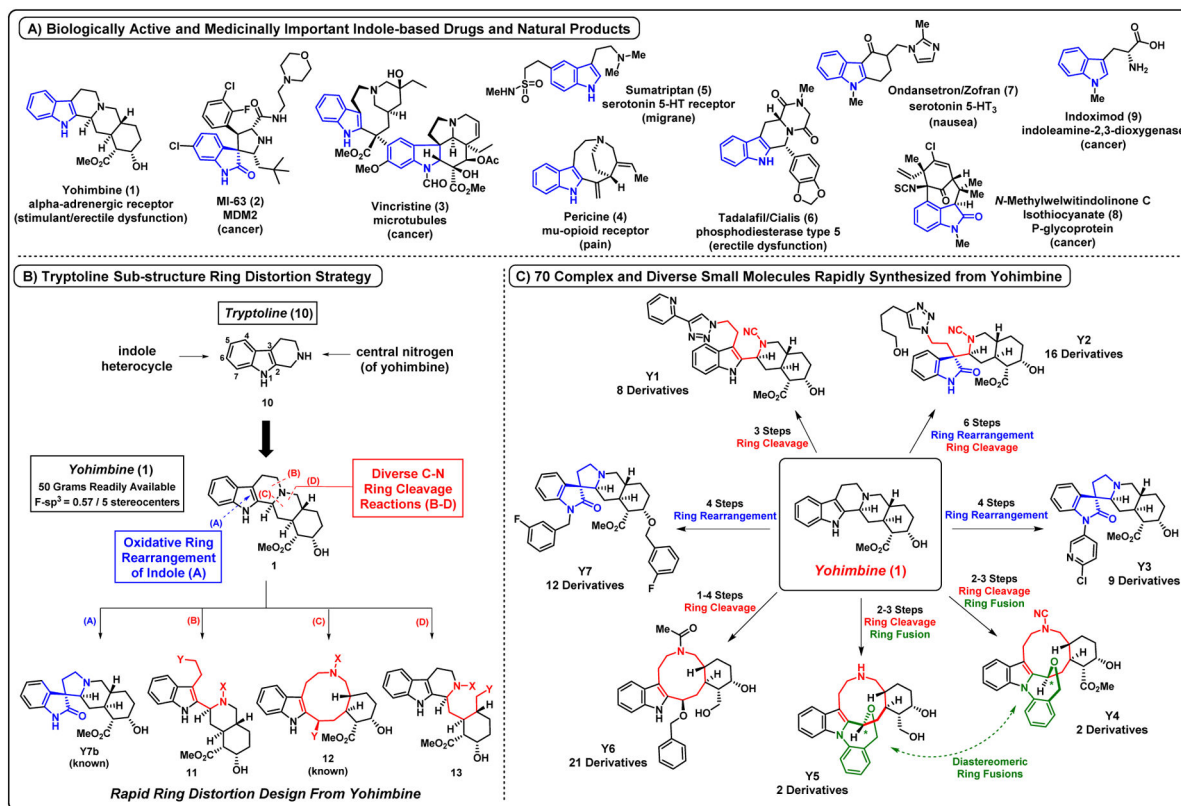
**Figure 1.**
A) Biologically active indole-containing and indole-related molecules. B) Tryptoline ring distortion strategy applied to the indole alkaloid Yohimbine. C) Complex and diverse small molecules rapidly synthesized from Yohimbine.
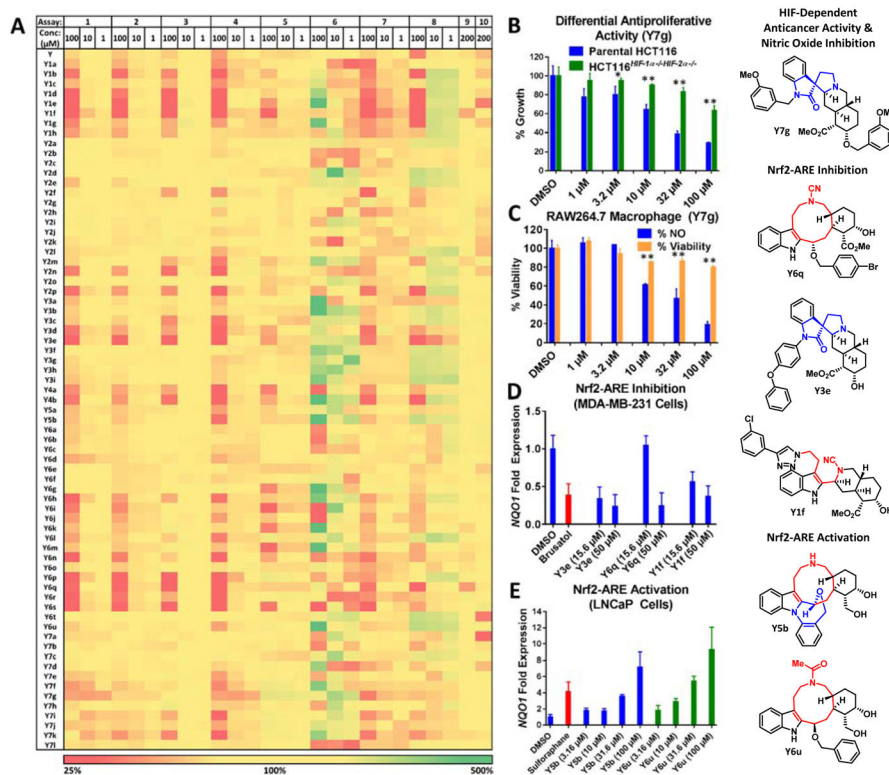
**Figure 2.**
A) Heat map matrix summarizing primary biological screening results of the yohimbine ring distortion library (biological activity scale key: red = inhibition; yellow = no change; green = activation), including the structures of six validated hit compounds. Rows correspond to compounds tested. Columns correspond to primary biological activity screens (1–10) and concentrations tested (200, 100, 10 and 1 μM). 1) Parental HCT116 and 2) HCT116$^{HIF-1a-/-HIF-2a-/-}$ cell viability; 3) RAW264.7 cell viability; 4) RAW264.7 NO production; 5) LNCaP cell viability; 6) LNCaP cell ARE activity; 7) MDA-MB-231-ARE-luc cell viability; 8) MDA-MB-231-ARE-luc cell ARE activity; 9) *S. aureus* and 10) *A. baumannii* growth. B) E) Validation experiments of hit compounds. B) HIF-dependent anticancer activity. Cell viability of parental HCT116 and HCT116$^{HIF-1a-/-HIF-2a-/-}$ cells was determined after 48 h exposure using MTT assay (*p*-values: 0.01 **, 0.05 *; pairwise student *t*-test comparing cell viability between parental HCT116 and HCT116$^{HIF-1a-/-HIF-2a-/-}$ cells at a given concentration). C) NO production and cell viability. Production of NO and cell viability of RAW264.7 cells were determined after 24 h exposure using Griess reagent and MTT assay, respectively (*p*-values: 0.01 **, 0.05 *; pairwise student *t*-test comparing relative NO production and viability of RAW264.7 cells at a given concentration). D) MDA-231-ARE-luc cell ARE activity and E) LNCaP cell ARE activity. ARE inhibition in MDA-MB-231-ARE-luc and ARE activation in LNCaP cells after 24 h exposure were validated by effects on endogenous *NQO1* transcript levels measured by RT-qPCR. *ACTB* expression was used as an internal control for normalization. All validation data are presented relative to vehicle control (0.5% DMSO). Brusatol (125

nM) and sulforaphane (10 μM) served as positive controls for MDA-MB-231-ARE-luc ARE inhibition and LNCaP ARE activation assays, respectively.
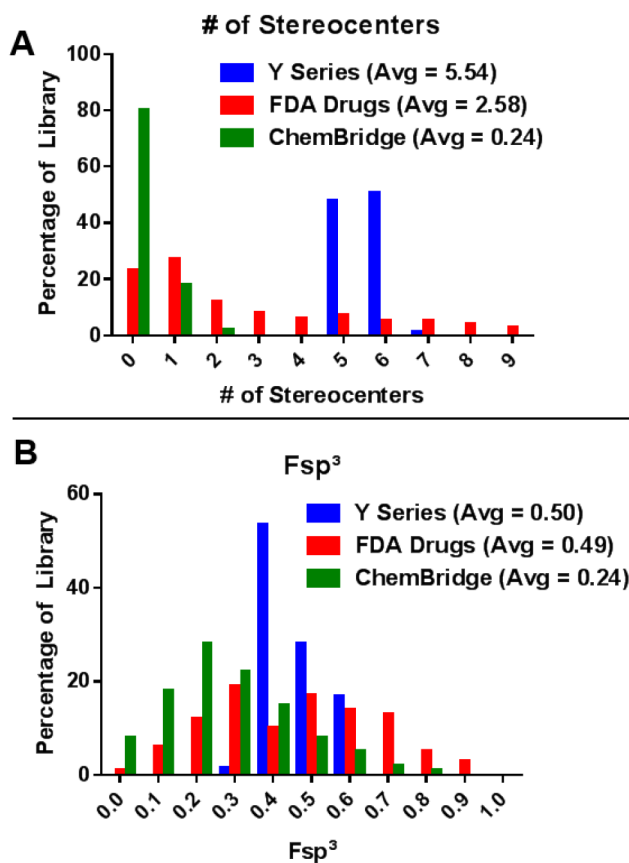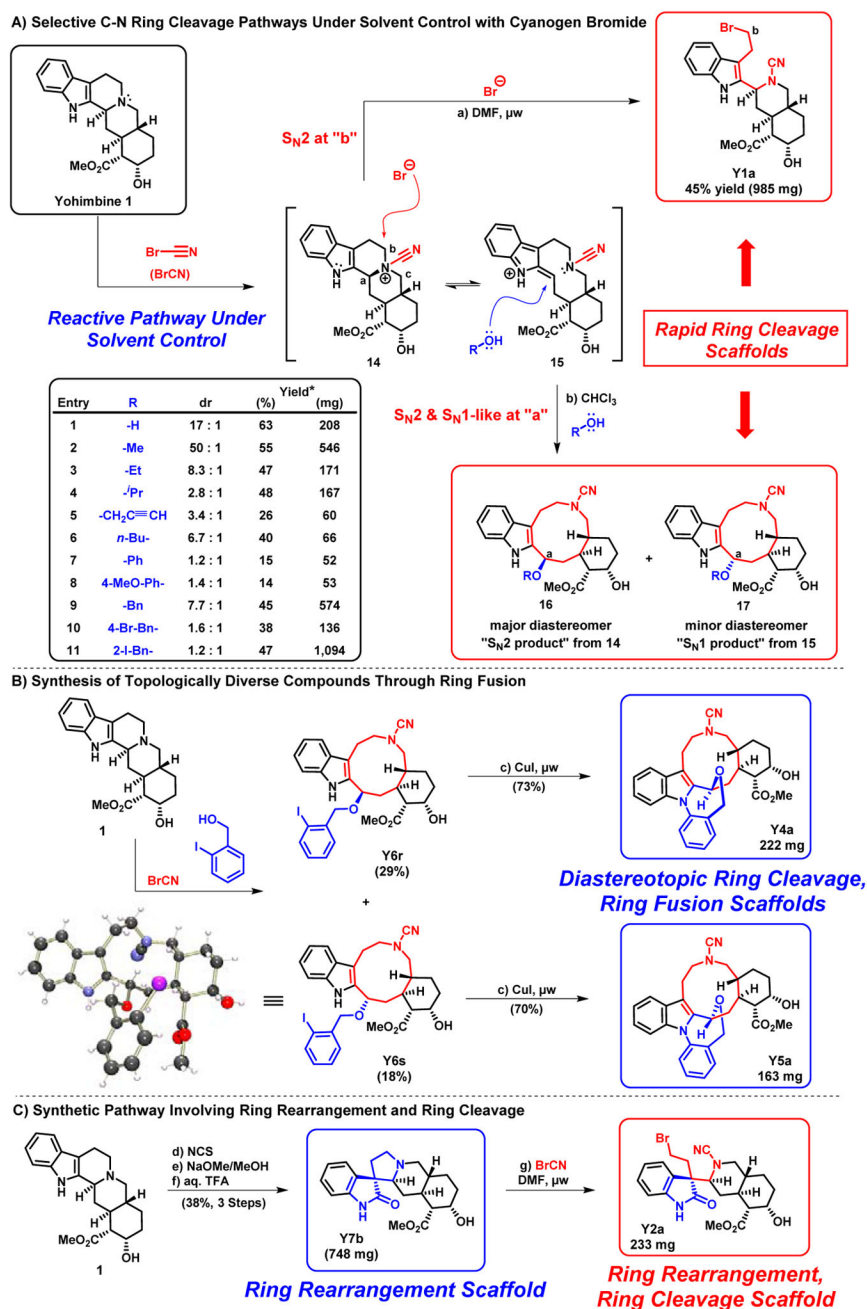
**Figure 3.**
A) Analysis of the stereochemical complexity of the yohimbine ring distortion library (Y Series) compared to FDA Drugs and a ChemBridge library. B) Comparison of the Fsp$^3$ character of the yohimbine library (Y Series), FDA Drugs and a ChemBridge library.

**Scheme 1.**

Summary of ring distortion from **1**. Reagents and Conditions: a) BrCN (3.0 eq.), DMF, μw, 100°C, 2.75 min, 45%; b) BrCN (3.0 eq.), ROH:CHCl$_3$ (3:1), rt, 16 h, 14 – 63% (11 examples); c) Copper(I) Iodide (0.35 eq.), K$_2$CO$_3$ (1.5 eq.), DMEDA (0.7 eq.), MeCN, μw, 160 °C, 13 min, 70 – 73%; d) NCS (1.1 eq.), CH$_2$Cl$_2$, –41 °C, 0.75 h, crude; e) 0.5 M NaOMe/MeOH, rt, 2.5 h, 66%; f) 10% TFA (aq), reflux, 1 h, 58%; g) BrCN (3.0 eq.), DMF, rt to 60 °C, 22 h, 52%. Notes: DMEDA = *N,N′*-dimethylethylenediamine, NCS = *N*-chlorosuccinimide. *Indicates combined percent yield and isolated yields of ether diastereomers.
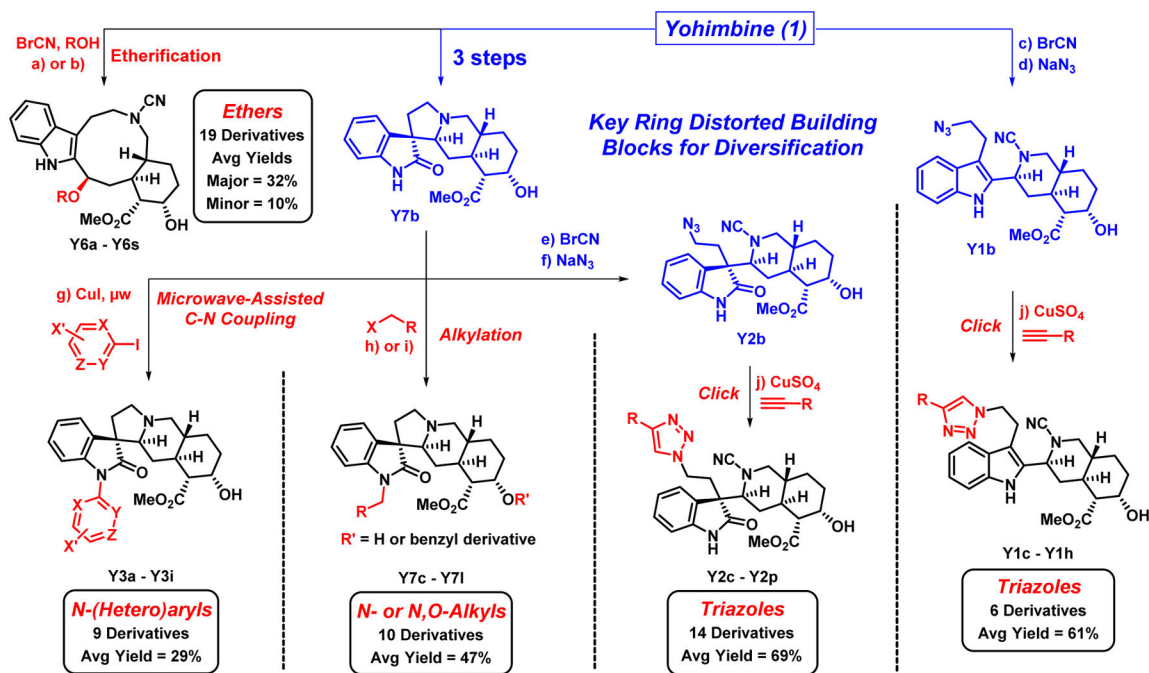
**Scheme 2.**

Library synthesis to afford sub-libraries of yohimbine ring-distorted compounds. Reagents and Conditions: a) BrCN (3.0 eq.), THF:H$_2$O (2.5:1), rt, 23 h, 57%; b) BrCN (3.0 eq), alcohol:CHCl$_3$ (1:3), rt (or reflux for **Y6j-Y6o**), 6.5 h (major diastereomer yields: 7 – 55%; minor diastereomer yields: 7 – 21%); c) BrCN (3.0 eq.), DMF, μw, 100 °C, 2.75 min, 56%; d) NaN$_3$ (3.0 eq.), DMF, rt to 75 °C, 22 h, 91%; e) BrCN (3.0 eq), DMF, rt to 60 °C, 22 h, 52%; f) NaN$_3$ (3.0 eq), DMF, rt to 80 °C, 16.5 h, 99%; g) Aryl iodide (1.1 eq.), DMEDA (0.70 eq.), CuI (0.35 eq.), MeCN, μw, 160 °C, 13 min, 20 – 37%; h) alkyl halide (1.9 eq.), K$_2$CO$_3$ (3.8 eq.), DMF, rt, 15 h, 44 – 80%; i) NaH (4.3 eq.), THF, 0 °C; then benzyl bromide (2.0 eq.), THF, 0 °C to rt, 16 h, 29 – 66%; j) alkyne (3.0 eq.), anhydrous CuSO$_4$ (0.5 eq.), sodium ascorbate (1.5 eq.), tBuOH:H$_2$O (1:2), CH$_2$Cl$_2$, rt, 2 h, Y1 yields: 19 – 78%, Y2 yields: 50 – 78%. BrCN = cyanogen bromide, DMEDA = *N,N*′-dimethylethylenediamine.