Article

Preliminary Structure–Activity Relationships and Biological Evaluation of Novel Antitubercular Indolecarboxamide Derivatives Against Drug-Susceptible and Drug-Resistant M. tuberculosis Strains

Oluseye K Onajole, Marco Pieroni, Suresh K Tipparaju, Shichun Lun, Jozef Stec, Gang Chen, Hendra Gunosewoyo, Haidan Guo, Nicole C Ammerman, William R. Bishai, and Alan P. Kozikowski

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jm4003878 • Publication Date (Web): 23 Apr 2013

Preliminary Structure–Activity Relationships and Biological Evaluation of Novel Antitubercular Indolecarboxamide Derivatives Against Drug-Susceptible and Drug-Resistant *M. tuberculosis* Strains

Oluseye K. Onajole,[†] Marco Pieroni,[†,^] Suresh K. Tipparaju,[†,§], Shichun Lun,[‖] Jozef Stec[†,⊥] Gang Chen,[†] Hendra Gunosewoyo,[†] Haidan Guo,[‖] Nicole C. Ammerman,[‖,▲] William R. Bishai[‖,▲,¶] and Alan P. Kozikowski.[†]**

[†]Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, Illinois, 60612, United States

[‖]Center for Tuberculosis Research, Department of Medicine, Division of Infectious Disease, Johns Hopkins School of Medicine, Baltimore, Maryland, 21231-1044, United States

[▲]KwaZulu-Natal Research Institute for Tuberculosis and HIV, Nelson R. Mandela School of Medicine, 719 Umbilo Road, Durban, 4001, KwaZulu-Natal, South Africa

[¶]Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, Maryland, 20815-6789, United States

ABSTRACT

Tuberculosis (TB) remains one of the leading causes of mortality and morbidity worldwide with approximately one third of the world's population infected with latent TB. This is further aggravated by HIV co-infection and the emergence of multidrug- and extensively drug-resistant (MDR and XDR, respectively) TB; hence the quest for highly effective antitubercular drugs with novel modes of action is imperative. We report herein the discovery of an indole-2-carboxamide analogue, **3**, as a highly potent antitubercular agent, and the subsequent chemical modifications aimed at establishing a preliminary body of structure–activity relationships (SARs). These efforts led to the identification of three molecules (**12–14**) possessing an exceptional activity in the low nanomolar range against actively replicating *Mycobacterium tuberculosis*, with minimum inhibitory concentration (MIC) values lower than those of the most prominent antitubercular agents currently in use. These compounds were also devoid of apparent toxicity to Vero cells. Importantly, compound **12** was found to be active against the tested XDR-TB strains and orally active in the serum inhibition titration assay.

INTRODUCTION

TB is a highly contagious and insidious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) and is currently the second leading cause of mortality due to infectious disease worldwide.[1] Despite its known etiology, TB still remains one of the most threatening health problems globally, claiming 1.4 million lives in 2011.[2] First-line TB chemotherapy options have not changed in nearly five decades with the most recent drug rifampin having been introduced in early 1960s.[3] The current treatment regimen for drug susceptible *M. tuberculosis* requires the

daily administration of first-line drugs which include ethambutol, isoniazid, pyrazinamide and rifampin for two months followed by an additional four months daily administration of isoniazid and rifampin.[4] However, several factors such as inconsistent treatment, patient non-compliance, and the non-availability of drugs during this period have contributed to the failure to achieve a cure, making the emergence of resistance an event practically unavoidable in many-resource-limited countries.[5]

Drug resistant-TB can be classified into two categories. MDR-TB is caused by infection with *M. tuberculosis* resistant to isoniazid and rifampin, and requires 18–24 months of combination therapy with second-line drugs which are generally more toxic, expensive and difficult to administer. XDR-TB is caused by *M. tuberculosis* resistant to isoniazid, rifampin, at least one fluoroquinolone and one of the injectable antitubercular drugs such as amikacin, kanamycin or capreomycin. The success rate for the treatment of XDR-TB is very low depending on the extent of drug resistance and whether or not the immune system of the patient is compromised. Consequently in the development of novel antitubercular chemotherapeutics, the lack of cross-resistance with existing drugs remains pivotal, along with good compound potency and little or no toxicity.[6]

At present, there are several drugs being evaluated in clinical trials for the treatment of TB.[7-9] Some of these represent novel chemical entities, such as TMC207 (**1**)[10] and PA824 (**2**)[11], whereas others are either approved drugs being repurposed for TB or they belong to known chemical series.[12-14] The United States Food and Drug Administration (FDA) recently approved TMC207 (bedaquiline, trade name Sirturo®)[15] for the treatment of MDR-TB (including XDR-TB) in adults, when no other treatment options are effective. This is the first antitubercular drug to be approved by the FDA in over four decades. Unfortunately, like other known second-line

antitubercular drugs, it has been reported to possess unwanted side effects, in particular its ability to cause QT (the time interval measured from the beginning of the QRS complex to the end of the T wave in an electrocardiogram) prolongation could potentially lead to abnormal heart rhythms.[15] A singular FDA approval in 40 years coupled with the staggering volume of mortality from TB underscore the impetus for the discovery and development of new TB chemotherapeutics.

In our continuous efforts to discover novel antitubercular scaffolds,[16-22] a phenotypic screening of a carefully selected library of 6800 compounds was carried out.[23] The overall physicochemical properties of this library fall within Lipinski's rules of 5, and thus are lead-like. The phenotypic screening of this library against replicating *M. tuberculosis* led to the identification of an indole-2-carboxamide scaffold (Figure 1) as one of the hit series.[22] The indole-2-carboxamide, **3**, was found to possess potent anti-TB activity (MIC = 0.93 μM) with low toxicity against Vero cells (half maximal inhibitory concentration [IC_{50}] > 200 μM). Studies on the identification of the molecular target for this class of indole-2-carboxamides using genome sequencing suggest that they may inhibit *M. tuberculosis* growth by acting on the MmpL3 protein, which belongs to the resistance, nodulation and cell division (RND) family of membrane transporters.[24] Herein we describe the synthesis, the *in vitro* biological evaluation, and bioavailability study of a number of indolecarboxamide analogues rationally designed so as to define a preliminary body of SAR as potential antitubercular agents.

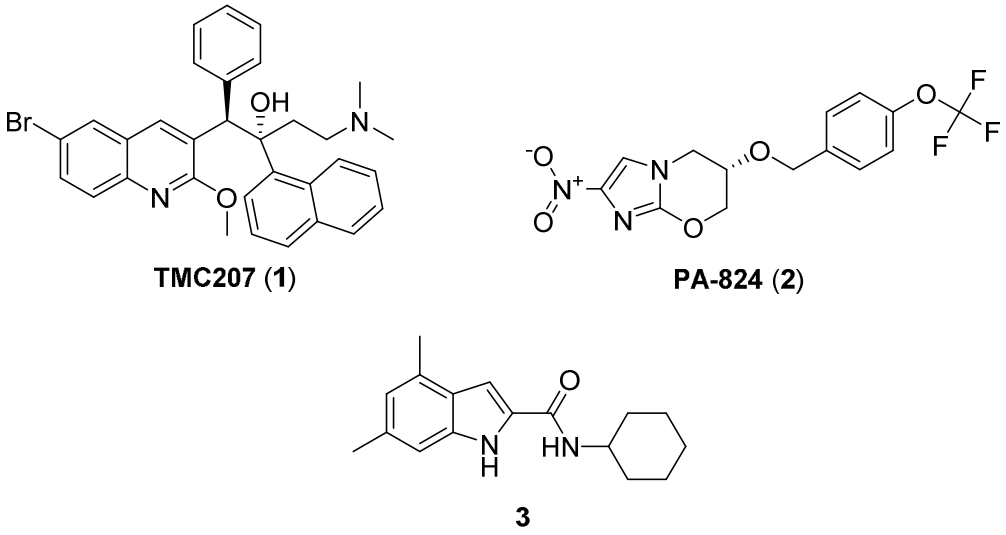


Figure 1. Structure of TMC207 (**1**), PA-824 (**2**) and hit compound **3**

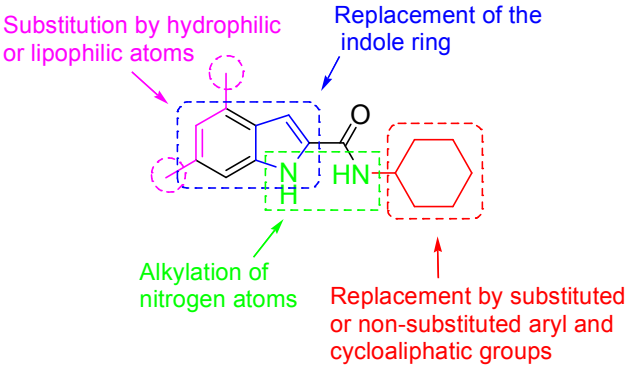


Figure 2. Strategies for modification of hit compound **3**

CHEMISTRY

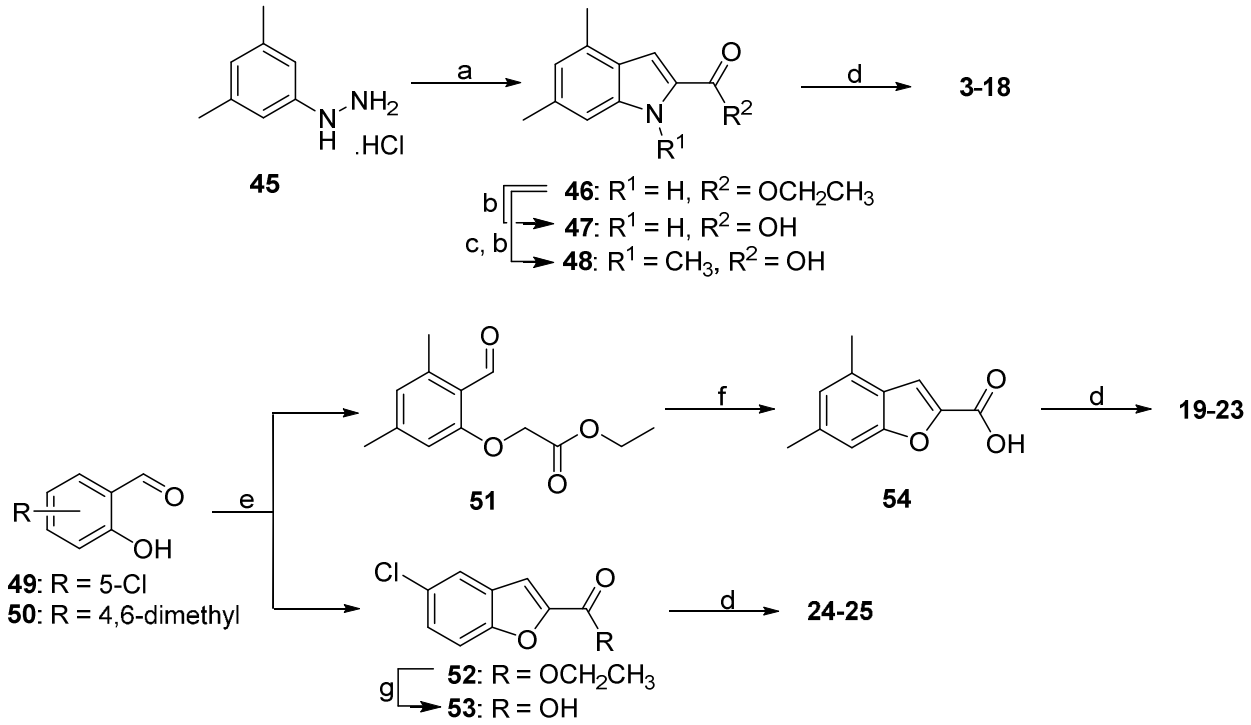
The hit compound **3** obtained from high throughput screening (HTS) was resynthesized to confirm the activity along with 40 novel derivatives (**4-44**) employing an efficient amide coupling protocol (Scheme 1 and 2). Briefly, following a Fischer indole synthesis protocol, 3,5-dimethylphenylhydrazine hydrochloride (**45**) was reacted with ethyl pyruvate under acidic conditions to afford the disubstituted indole-2-carboxylate **46**, and subsequent basic hydrolysis afforded the corresponding acid **47**. *N*-methylation of **46** followed by basic hydrolysis gave the

carboxylic acid **48**. The carboxylic acids were subsequently reacted with their corresponding amine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and hydroxybenzotriazole (HOBt) as coupling agents and triethylamine as a base to obtain compounds **3**–**18** (Scheme 1). 5-Chlorobenzofuran-2-carboxylic acid (**53**)[25] and 4,6-dimethylbenzofuran-2-carboxylic acid (**54**)[26] were obtained following a modified literature protocol (Scheme 1).[27,28] Compound **54** was reacted with the appropriate amines under standard amide coupling conditions to obtain compounds **19**–**23**. Following similar conditions, compounds **24** and **25** were obtained by reacting carboxylic acid **53** with the appropriate amines (Scheme 1).

The unsubstituted and monosubstituted carboxylic acids (**55**–**59**) were reacted with their corresponding amines to afford compounds **26**–**31**, **33** and **34** while compound **32** was obtained from its methoxy precursor **30** using boron tribromide (Scheme 2). 3,5-Bis(trifluoromethyl)phenylhydrazine hydrochloride (**60**) was reacted with ethyl pyruvate under microwave irradiation to obtain its hydrazone intermediate **61**, which was further subjected to acidic conditions to obtain the cyclized indole (**62**). Basic hydrolysis then afforded the desired carboxylic acid **63**. Compound **63** was reacted with cycloheptylamine or cyclooctylamine to provide the amides **35** and **36**. 3,5-Dimethylbenzene-1,2-diamine (**64**) was reacted with methyl-2,2,2-trichloroacetimidate to afford its trichloromethyl intermediate **65**, followed by basic hydrolysis to give the corresponding acid **66**. Decarboxylation of indole **47** with copper powder in quinoline gave the desired intermediate **67**, which was subsequently reacted with trichloroacetyl chloride to give the trichloromethyl intermediate **68**. Subsequent basic hydrolysis afforded 4,6-dimethyl-1*H*-indole-3-carboxylic acid (**69**). Compounds **66** and **69** were reacted

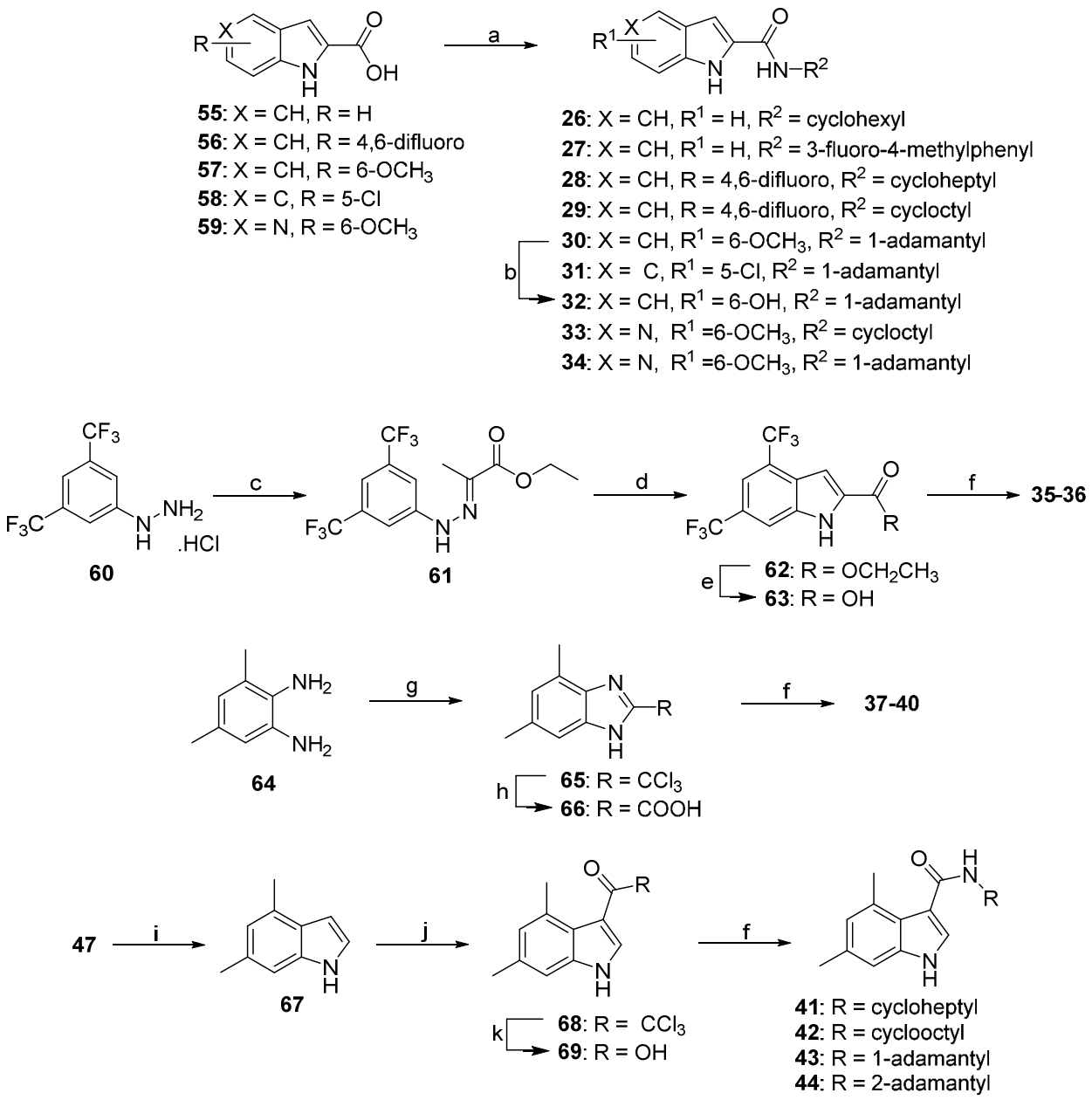
with their corresponding amines under standard amide coupling conditions to obtain compounds **37**–**44** (Scheme 2).

Scheme 1[a]



[a]Reagents and conditions: (a) ethyl pyruvate, *p*-TsOH, toluene, reflux, overnight; (b) LiOH, EtOH, reflux, 3 h; (c) CH_3I, NaH, DMF, rt; (d) EDC·HCl, HOBt, corresponding amines, Et_3N, CH_2Cl_2, rt, 12–16 h; (e) ethyl bromoacetate, K_2CO_3, 140 °C, 6 h; (f) (i) EtOH, C_2H_5ONa, rt to 70 °C, 1 h (ii) 3N NaOH, 70 °C, 20 min (iii) 1N HCl, rt; (g) THF/EtOH (1:1), 3N NaOH, rt, 3–4 h.

Scheme 2[a]



[a]Reagents and conditions: (a) EDC·HCl, HOBt, corresponding amines, Et_3N, CH_2Cl_2, rt, 12–16 h; (b) BBr_3, CH_2Cl_2, -78 °C to rt, 3 h; (c) ethyl pyruvate, EtOH, MW, 150 °C, 10 min; (d) polyphosphoric acid, toluene, reflux, 3 h; (e) LiOH, EtOH, reflux, 3 h; (f) EDC·HCl, HOBt, corresponding amines, *N*-methylmorpholine, DMF, rt, 12–16 h; (g) acetic acid, methyl-2,2,2-

trichloroacetimidate, rt, 16 h; (h) THF, 1N NaOH, rt, 3–4 h; (i) Cu powder, quinoline, 240 °C, 3 h; (j) trichloroacetyl chloride, C_5H_5N, CH_2Cl_2, 3 h; (k) 2N KOH, THF, rt, 3 h.

RESULTS AND DISCUSSION

The general strategy for the chemical modifications of the hit compound **3** aimed at improving the antitubercular activity is summarized in Figure 2. The SAR investigation was focused on the role of different substituents on the amide nitrogen, the indole nitrogen, replacement of the indole core with other heterocycles, substitution at the 3-position of the indole ring, and on the benzene ring of the indole group (Figure 2). Target compounds **3–44** were screened *in vitro* against the *M. tuberculosis* strain H37Rv to obtain the MIC values using the microplate Alamar Blue assay (MABA) while cytotoxicity was assessed for selected compounds using Vero cells.

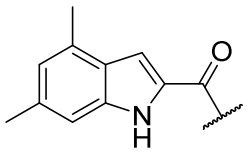
The initial round of SAR modifications was directed towards substitutions for the cyclohexyl group while maintaining the 4,6-dimethyl-1*H*-indole-2-carboxamide scaffold. First, we substituted the cyclohexyl group for an unsubstituted benzene ring to ascertain the possibility of π–π stacking interactions with the biological target as well as the impact of the planarity of the aromatic ring on activity. Compounds **4** (MIC = 3.8 μM) and **5** (MIC = 1.7 μM) were approximately 4-fold and 2-fold less active than the hit compound **3** (MIC = 0.93 μM), respectively, while the pyridine analog **6** (MIC = 240 μM) showed a dramatic loss in activity. These results suggest that the presence of an aromatic ring on the amide nitrogen is not favorable. The nitrogen-containing cycloaliphatic groups (**7**, MIC = 449 μM; **8**, MIC = 204 μM, and **9**, MIC = 428 μM) were subsequently tested for their antitubercular activity. However, none of these analogs were found to be active, therefore implying that hydrophilic substituents are

generally not favorable for biological activity. This trend also includes the pyridyl analog **6**, which was 63-fold less active compared to the phenyl derivative **4**.

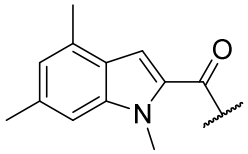
Based on these data, the next iteration was performed to examine cycloaliphatic rings. The introduction of a small ring, such as cyclopropyl, led to a complete loss of activity (**10**, MIC = 561 μM) whereas a bulkier substituent, such as the cycloheptyl, yielded a highly active compound (**11**, MIC = 0.055 μM). Of particular note, compound **11** is approximately 5-fold more potent than INH (MIC = 0.29 μM), the standard first-line drug used against actively replicating *M. tuberculosis*, and it is comparable in activity to the antitubercular agents now on the market or in clinical trials, namely TMC207 (**1**) (MIC = 0.05 μM)[10] and PA824 (**2**) (MIC = 0.04–0.70 μM).[11] Once it was established that a bulky cycloaliphatic ring on the amide nitrogen plays an important role for activity, the cyclooctyl and the adamantyl rings were introduced (analogs **12–14**). These modifications led to the identification of the most active compounds in the series (**12**–**14**), with MIC values of 0.013 μM (**12**) and 0.012 μM (**13** and **14**), respectively (Table 1), which are approximately 3- to 4-fold lower than those published for TMC207 (**1**)[10] and PA824 (**2**).[11] Furthermore, the addition of a methylene spacer between the amide nitrogen and the cycloaliphatic ring was tolerated (compound **15**, MIC = 0.88 μM). Although the increase in activity was accompanied by a rise in the lipophilicity [the ClogD (pH = 7.4) values calculated using the ACD/Percepta software are as follow: **3** = 4.36; **11** = 4.78; **12** = 5.32; **13** = 5.03; **14** = 4.96], it must be considered that TMC207 (**1**) (Sirturo®), recently approved by the FDA for treatment of MDR-TB, has a CLogD value of 5.32. These findings lead us to hypothesize that a rather large hydrophobic pocket may be present in the target binding site within proximity of the amide moiety, which is able to accommodate bulky groups such as the cyclooctyl and adamantyl groups. More importantly, compounds **11**–**14** exhibited high selectivity indices (SI) ranging from

>3,600 for **11** and **12** to >16,600 for **13** and **14** when tested against Vero cells, indicating that these compounds lack apparent cyctoxicity in this system.

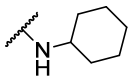
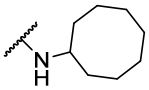
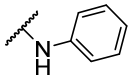
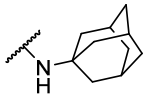
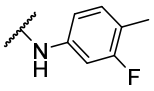
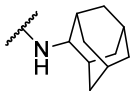
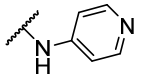
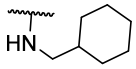
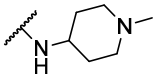
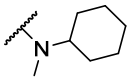
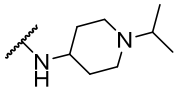
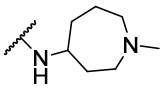
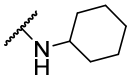
Table 1. Antitubercular activity of compounds **3**–**18** against the *M. tuberculosis* strain H37Rv.

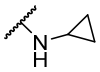
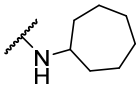


3-17



18

Compd	R	MIC[a] (μM)	IC_{50}[b] (μM)	Compd	R	MIC[a] (μM)	IC_{50}[b] (μM)
3		0.93	>200	12		0.013	54
4		3.8	>200	13		0.012	>200
5		1.7	>200	14		0.012	>200
6		240	NT[c]	15		0.88	>200
7		448	NT	16		450	NT
8		204	NT	17		>499	NT
9		428	NT	18		450	NT

10		561	NT	INH[d]		0.29	NT
11		0.055	>200				

[a]The lowest concentration of drug leading to at least a 90% reduction of bacterial growth signal by the microplate Alamar Blue assay (MABA). MIC values are reported as an average of three individual measurements; [b]cytotoxicity against Vero cells; [c]NT = not tested; [d]INH = Isoniazid.

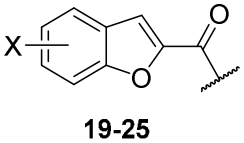
The importance of hydrogen bond donors on the indoleamide core for potent antitubercular activity was also investigated. First, the influence of the hydrogen atom on the amide motif was explored; this led to the synthesis of compounds **16** and **17**, which were bereft of anti-TB activities (MIC values of > 400 μM, Table 1). Secondly, *N*-methyl indole analogue **18** (MIC = 450 μM) was approximately 500-fold less potent than the corresponding analogue **3** (MIC = 0.93 μM), and replacement of the indole moiety with a benzofuran (**19**–**21** *vs* **11**–**13**) resulted in a dramatic attenuation of activity, ranging from ~250 up to 2,000-fold difference (Table 2). The other synthesized benzofuran analogues **22**–**24** had MIC values of 113, 59 and 26 μM respectively, while analogue **25** (MIC = >388 μM) was found to be > 1,000-fold less potent than the indole counterpart **31**[29] (MIC = 0.38 μM). These data highlight the importance of the two NH groups at the indole and amide moieties for potent anti-TB activity.

Subsequent SAR investigation was focused on the effects of indole substituents on anti-TB activity (Table 2). Interestingly, 4,6-didesmethyl indole analogues (**26** and **27**) were found to be devoid of activity (MIC = ~500 μM) while replacement of the methyl groups with fluoro- (**28** and **29**) or trifluoromethyl- (**35** and **36**) substituents resulted in a 3- to 17- fold drop in activity

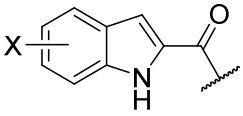
compared to their counterparts **11** and **12**. Introduction of a methoxy group at C-6 (**30**, MIC = 0.77 μM) gave a 2-fold higher activity than a chlorine atom at C-5 (**31**, MIC = 0.38 μM), whereas the more polar 6-hydroxy substituent (**32**, MIC = 12.9 μM), resulted in 17-fold reduction of activity compared to **30**. Thus far, the 4,6-dimethyl substituents on the indole ring resulted in compounds with the most potent anti-TB activity in this series.

Aiming to improve the water solubility by introduction of ionizable nitrogen groups, the 5-aza-6-methoxyindoles **33** and **34** were synthesized whereby the benzene ring of the indole nucleus was replaced with a pyridine ring. Unfortunately, these modifications resulted in a 510-fold and a 125-fold decrease in activity, respectively, compared to the MIC values of compounds **12** and **13**. Further attempts to replace the indole core included the replacement with benzo[*d*]imidazole (**37**–**40**). However, these compounds did not show improved antitubercular activity compared to their corresponding indole-2-carboxamide counterparts **11**–**14**. The positioning of the carboxamide on the indole ring was also explored (Scheme 2). Shifting the carboxamide moiety to position 3 of the indole ring (**41**–**44**, Scheme 2) resulted in a drastic drop in the activity (MIC values of ~ 200 μM), supporting the importance of the carboxamide group at position 2 of the indole ring. Thus, these data point to the indole-2-carboxamide core as the superior scaffold for potent and non-toxic anti-TB leads.

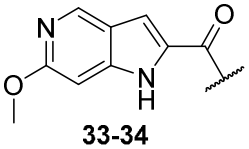
Table 2. Antitubercular activity of compounds **19**–**40** against *M. tuberculosis* strain H37Rv.



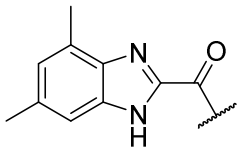
19-25



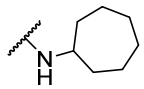
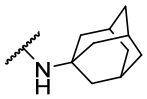
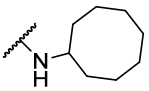
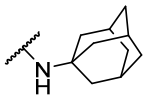
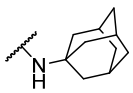
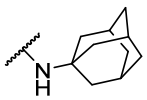
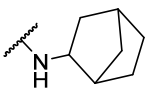
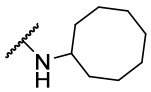
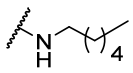
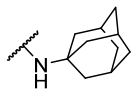
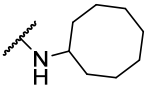
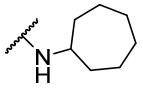
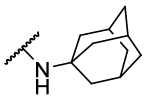
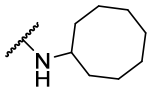
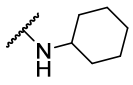
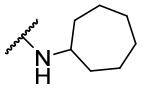
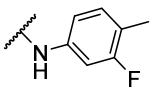
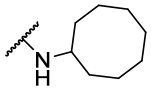
26-32, 35-36

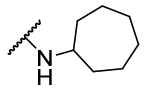
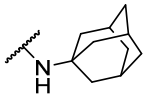
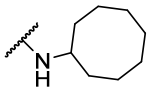
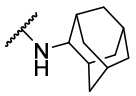


33-34



37-40

Compd	X	R	MIC[a] (μM)	Compd	X	R	MIC[a] (μM)
19	4,6-dimethyl		56	**30**	6-OCH_3		0.77
20	4,6-dimethyl		27	**31**	5-Cl		0.38
21	4,6-dimethyl		3.1	**32**	6-OH		13
22	4,6-dimethyl		113	**33**	-		6.6
23	4,6-dimethyl		59	**34**	-		1.5
24	5-Cl		26	**35**	4,6-bis(CF_3)		0.64
25	5-Cl		≥388	**36**	4,6-bis(CF_3)		0.04
26	H		>528	**37**	-		>224
27	H		477	**38**	-		1.7

28	4,6-difluoro		0.86	**39**	-		0.39
29	4,6-difluoro		0.10	**40**	-		1.5

[a]The lowest concentration of drug leading to at least a 90% reduction of bacterial growth signal by microplate Alamar Blue assay (MABA). MIC values are reported as an average of three individual measurements.

Table 3. Antitubercular activity of compound **3**, **11** and **12** against susceptible, MDR and XDR strains of *M. tuberculosis*.

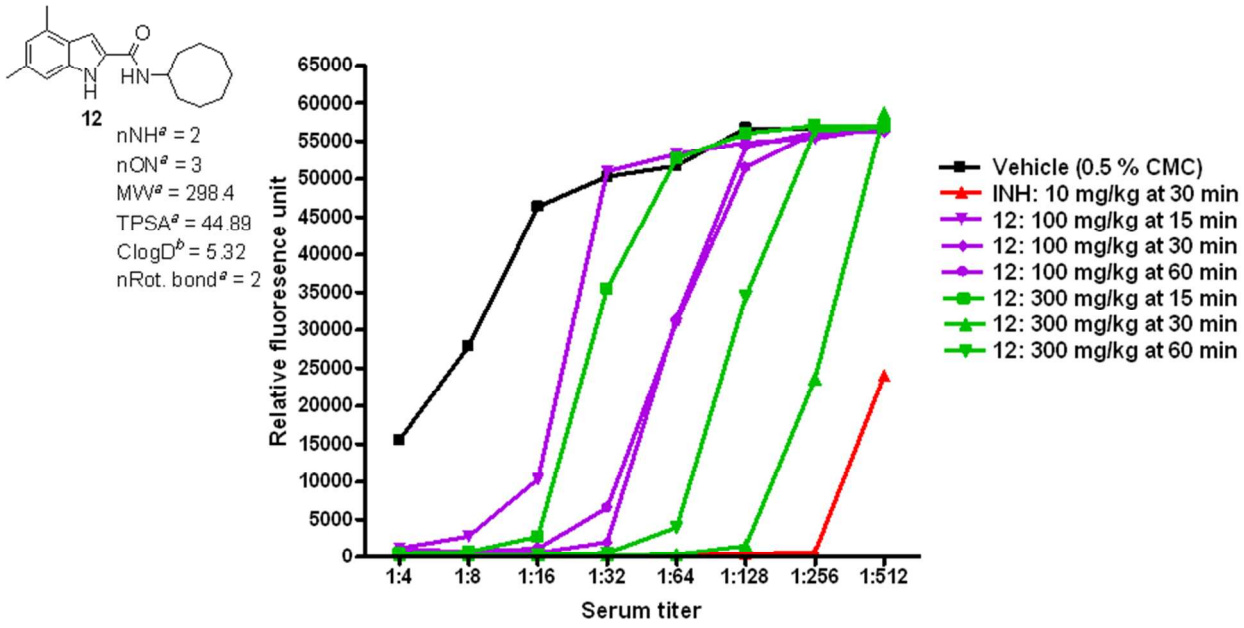
Compd	V4207 (DS)[a]	TF274 (XDR)[b]	R506 (XDR)[b]	KZN494 (MDR)[c]	V2475 (MDR)[c]
	MIC[d] (μM)				
3	0.93	0.46	0.46	3.7	0.93-1.9
11	0.11	0.055	0.055	0.11	0.11
12	0.026	0.026	0.0067	[e]NT	[e]NT

[a]Drug susceptible strain of *M. tuberculosis*; [b]extensively drug resistant strain of *M. tuberculosis*; [c]multi-drug resistant strain of *M. tuberculosis*; [d]the lowest concentration of drug leading to at least a 90% reduction of bacterial growth signal by microplate Alamar Blue assay (MABA); reported MIC values are an average of three individual measurements; [e]NT = not tested.

Selected compounds **3**, **11** and **12** were tested for their ability to inhibit the growth of the acquired clinical MDR-TB (KZN494 and V2475) and XDR-TB (TF274 and R506) strains from

KwaZulu-Natal, South Africa (Table 3).[30] To our delight, these indole-2-carboxamides maintained similar excellent activities against the susceptible *M. tuberculosis* strain $H_{37}Rv$ in all the tested drug-resistant strains.

Figure 3. Serum inhibition titration result for compound **12**.



nNH = number of hydrogen bond donors; nON = number of hydrogen bond acceptors; MW = Molecular Weight; TPSA = Topological polar surface area; nRot. bond = number of rotatable bonds calculated using the molinspiration online service (www.molinspiration.com); ClogD was calculated using the ACD/lab Percepta software; BALB/c mice were orally gavaged with two doses (100 and 300 mg/kg) of compound **12**, with blood collected at different time points and serum separated 60 min later. Growth inhibition of serially diluted serum on H37Rv was determined using the Alamar Blue assay; Vehicle, 0.5 % CMC (carboxylmethyl cellulose); INH, isoniazid at 10 mg/kg (positive control).

The most potent indole-2-carboxamides **11**–**14** were evaluated in the serum inhibition titration assay.[31] Briefly, each compound was administered at 100 and 300 mg/kg to BALB/c mice by oral gavage using carboxymethyl cellulose as vehicle, after which blood samples were collected at 15, 30 and 60 minutes. The sera were separated and prepared in 2-fold dilutions and incubated with a bacterial suspension for 7 days. Bacterial growth was measured using MABA. As illustrated in Figure 3, the cyclooctyl derivative **12** was present in the serum at potent concentrations up to a 1:128 dilution following a 300 mg/kg oral dose at the 30 minute time point. In contrast, the cycloheptyl derivative **11** and both adamantyl derivatives **13** and **14** were not active (data not shown) in this assay which may be a consequence of any of a number of factors including poor absorption, tight serum protein binding, rapid metabolism, etc.[32] The attractive results achieved with compound **12** suggest that it or one of its analogs may be worth developing further in order to identify potential anti-TB chemotherapeutics.

CONCLUSIONS

A set of indolecarboxamide derivatives **3–44** has been synthesized and evaluated to build a body of preliminary SAR based on compound **3** obtained from an high-throughput screening campaign. The SAR of these analogues leads to the following considerations for anti-TB activity: *a)* at the amide nitrogen, lipophilic and bulky substituents are beneficial for potent anti-TB activity (**12**–**14**), whereas polar substituents (**6–9**) lead to loss of the activity suggesting the presence of a hydrophobic pocket in the target binding site; *b)* carboxamide substitution at position 2 of the indole ring is essential in retaining the anti-TB activity; *c)* an unsubstituted indole nitrogen and a mono-substituted amide nitrogen are required for the antimycobacterial activity; *d)* methyl groups at position C-4 and C-6 of the indole ring are important in order to

confer high activity. The most active compounds in the series, **12**–**14**, have MIC values lower than that of isoniazid, the most active compound used against actively replicating *M. tuberculosis*, and those of TMC207 (**1**)[10] and PA824 (**2**).[11] In addition, compounds **3**, **11** and **12** showed excellent activity against the susceptible, the MDR- and the XDR-TB strains, indicating that this series does not suffer from cross-resistance with first- and second-line TB drugs. In particular, compound **12** was found to be orally active in the serum inhibition titration assay. Overall, the extraordinary potency against drug susceptible as well as drug-resistant *M. tuberculosis* strains, and the lack of apparent toxicity, establish these indole-2-carboxamides derivatives as promising novel class of compounds in the pursuit of highly effective anti-TB agents.

EXPERIMENTAL SECTION

General information. The following carboxylic acids, 1*H*-indole-2-carboxylic acid, 5-chloro-1*H*-indole-2-carboxylic acid, 6-methoxy-l*H*-indole-2-carboxylic acid, were purchased from Sigma-Aldrich while 6-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxylic acid and 4,6-difluoro-1*H*-indole-2-carboxylic acid were purchased from Chem-Impex and Combi-blocks. Anhydrous dichloromethane (CH_2Cl_2) was obtained by distillation over calcium hydride. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz, respectively, with TMS as an internal standard. Standard abbreviation indicating multiplicity was used as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, m = multiplet and br = broad. HRMS experiments were performed on Q-TOF-2TM (Micromass) and IT-TOF (Shimadzu) instruments. TLC was performed with Merck 60 F254 silica gel plates. Flash chromatography was performed using CombiFlash® Rf system with RediSep® columns or

alternatively using Merck silica gel (40–60 mesh). Final compounds were purified by preparative HPLC unless otherwise stated. The preparative HPLC employed an ACE 5-AQ (21.2 mm × 150 mm) column, with detection at 254 and 280 nm on a Shimadzu SCL-10A VP detector, flow rate = 17.0 mL/min. Method 1: 50–100% CH_3OH/H_2O in 30 min; 100% CH_3OH in 5 min; 100–50% CH_3OH/H_2O in 4 min. Method 2: 25–100% CH_3OH/H_2O in 30 min; 100% CH_3OH in 5 min; 100–25% CH_3OH/H_2O in 4 min. Method 3: 15-100% CH_3OH/H_2O in 30 min; 100% CH_3OH in 5 min; 100–15% CH_3OH/H_2O in 4 min. Both solvents contains 0.05 vol % of trifluoroacetic acid (TFA). Purities of final compounds were established by analytical HPLC, which was carried out using the Agilent 1100 HPLC system with a Synergi 4 μm Hydro-RP 80A column, on a variable wavelength detector G1314A. Method 1: flow rate = 1.4 mL/min; gradient elution over 20 minutes, from 30% MeOH-H_2O to 100% MeOH with 0.05% TFA. Method 2: flow rate = 1.4 mL/min; gradient elution over 20 minutes, from 50% MeOH-H_2O to 70% MeOH with 0.05% TFA. The purity of all tested compounds was >95% as determined by the method described above.

General procedure for the synthesis of 3–44

To a solution of the appropriate carboxylic acid (1 equiv) in anhydrous dichloromethane (CH_2Cl_2) or dimethylformamide (DMF) (4 mL/mmol) at room temperature were added anhydrous hydroxybenzotriazole (HOBt, 1 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride **(**EDC.HCl, 1 equiv) under an argon atmosphere. After stirring for 10 min, the appropriate substituted amine (1 equiv) and triethylamine or *N*-methyl morpholine (1.5 equiv) were added, and the reaction mixture was stirred at room temperature until disappearance of the starting material (usually 12 to 16 h). After this time water (2 mL) was added, and the mixture was extracted with EtOAc (3×10 mL), the

organic layers were separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–hexane 1:4 unless specified differently) to obtain the indoleamides in yields ranging from 34 to 95%.

***N*-Cyclohexyl-4,6-dimethyl-1*H*-indole-2-carboxamide (3).** Yield 92% (white powder). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 7.07 (s, 1H), 6.79 (s, 2H), 6.03 (d, J = 7.6 Hz, 1H), 4.07–3.98 (m, 1H), 2.44 (s, 3H), 2.37 (s, 3H), 2.10–2.06 (m, 2H), 1.83–1.78 (m, 2H), 1.68–1.45 (m, 2H), 1.31–1.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 136.5, 134.6, 130.9, 129.9, 125.7, 122.7, 109.2, 99.9, 48.5, 33.3, 25.6, 24.9, 21.8, 18.6. HRMS (ESI) calcd for $C_{17}H_{22}N_2O$ ($[M+H]^+$) 271.1805; found: 271.1809.

***N*-Phenyl-4,6-dimethyl-1*H*-indole-2-carboxamide (4).** Yield 67% (white powder). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 7.89 (br s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.83 (s, 1H), 2.56 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 139.2, 137.2, 133.3, 130.3, 128.7, 125.3, 123.4, 122.0, 120.0, 109.6, 102.7, 99.6, 21.6, 18.5. HRMS (ESI) calcd for $C_{17}H_{16}N_2O$ ($[M+H]^+$) 265.1335; found: 265.1348

***N*-(3-Fluoro-4-methylphenyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (5).** Yield 89% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.61 (s, 1H), 10.26 (s, 1H), 7.80 (d, J = 12.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.11 (s, 1H), 6.70 (s, 1H), 2.50 (s, 3H), 2.21 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.5 (J = 239 Hz), 159.9, 138.6 (J = 11 Hz), 137.3, 133.4, 131.3 (J = 6.3 Hz), 130.3, 130.0, 125.3, 122.0, 118.6 (J = 17.2 Hz), 115.5, 109.6, 106.7 (J = 27 Hz), 102.8, 21.5, 18.4, 13.7 (J = 2.9 Hz). HRMS (ESI) calcd for $C_{18}H_{17}FN_2O$ ($[M+H]^+$) 297.1252; found: 297.1266.

***N*-(4-Pyridinyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (6).** Yield 77% (white powder). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J = 5.2 Hz, 2H), 7.88 (d, J = 6.3 Hz, 2H), 7.43 (s, 1H), 7.27 (s, 1H), 6.87 (s, 1H), 2.54 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.6, 150.4, 145.9, 137.6, 133.9, 130.6, 129.5, 125.2, 122.3, 113.7, 109.7, 103.8, 99.6, 21.6, 18.5. HRMS (ESI) calcd for $C_{16}H_{15}N_3O$ ($[M+H]^+$) 266.1288; found: 266.1295.

***N*-(1-Methyl-4-piperidinyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (7).** Purified by column chromatography (EtOAc–hexane 1:1). Yield 65% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.24 (s, 1H), 8.18 (d, J = 8 Hz, 1H), 7.13 (s, 1H), 7.02 (s, 1H), 6.58 (s, 1H), 3.76–3.70 (m, 1H), 2.78–2.75 (m, 2H), 2.43 (s, 3H), 2.33 (s, 3H), 2.16 (s, 3H), 2.00–1.91 (m, 2H), 1.77 (m, 2H), 1.65-1.47 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.6, 136.7, 132.5, 130.7, 129.9, 125.3, 121.7, 109.5, 101.4, 54.6, 46.1, 31.7, 21.6, 18.5. HRMS (ESI) calcd for $C_{17}H_{23}N_3O$ ($[M+H]^+$) 286.1914; found: 286.1908.

***N*-(1-Isopropyl-4-piperidinyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (8).** Yield 70% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.43 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.02 (s, 1H), 6.66 (s, 1H), 3.74–3.72 (m, 1H), 2.81–2.78 (m, 2H), 2.70 (m, 1H), 2.43 (s, 3H), 2.33 (s, 3H), 2.17 (t, J = 12.0 Hz, 2H), 1.97–1.81 (m, 2H), 1.56–1.48 (m, 2H), 0.97 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.5, 136.7, 132.5, 130.7, 129.9, 125.3, 121.7, 109.5, 101.3, 53.7, 47.4, 47.0, 32.2, 21.6, 18.5, 18.2. HRMS (ESI) calcd for $C_{19}H_{27}N_3O$ ($[M+H]^+$) 314.2227; found: 314.2216.

***N*-(1-Methyl-4-azepanyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (9).** Yield 83% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.37 (s, 1H), 9.50 (br s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 7.00 (s, 1H), 6.57 (s, 1H), 4.17 (br s, 1H), 3.00–3.70 (m, 4H), 2.82 (s, 3H), 2.47 (s, 3H), 2.33 (s, 3H), 2.07–1.68 (m, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.4, 136.7,

132.7, 130.4, 130.0, 125.2, 121.8, 109.5, 101.5, 52.5, 48.1, 47.1, 43.8, 32.2, 21.6, 18.5. HRMS (ESI) calcd for $C_{18}H_{25}N_3O$ ($[M+H]^+$) 300.2070; found: 300.2068.

***N*-Cyclopropyl-4,6-dimethyl-1*H*-indole-2-carboxamide (10)**. Yield 95% (white powder). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (br s, 1H), 7.07 (s, 1H), 6.79 (s, 2H), 6.43 (s, 1H), 3.11–2.92 (m, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 0.94–0.88 (m, 2H), 0.76–0.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 137.1, 133.0, 130.9, 130.3, 125.7, 122.1, 109.9, 101.7, 23.1, 21.9, 18.8, 6.2. HRMS (ESI) calcd for $C_{14}H_{16}N_2O$ ($[M+H]^+$) 229.1335; found: 229.1342.

***N*-Cycloheptyl-4,6-dimethyl-1*H*-indole-2-carboxamide (11).** Yield 72% (white powder). ^{1}H NMR (400 MHz, CD_3OD) δ 7.12 (s, 1H), 7.05 (s, 1H), 6.70 (s, 1H), 4.09–4.04 (m, 1H), 2.48 (s, 3H), 2.38 (s, 3H), 2.00–1.98 (m, 2H), 1.76–1.54 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 135.2, 131.8, 128.5, 127.9, 123.7, 119.8, 106.9, 99.8, 48.9, 32.7, 25.8, 22.2, 18.6, 15.4. HRMS (ESI) calcd for $C_{18}H_{24}N_2O$ ($[M+H]^+$) 285.1889; found: 285.1892.

***N*-Cyclooctyl-4,6-dimethyl-1*H*-indole-2-carboxamide (12).** Yield 83% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.29 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 1.6 Hz, 1H), 7.02 (s, 1H), 6.66 (s, 1H), 4.06–4.01 (m, 1H), 2.44 (s, 3H), 2.34 (s, 3H), 1.81–1.65 (m, 6H), 1.61–1.51 (m, 8H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.9, 134.4, 131.1, 127.7, 127.1, 122.6, 119.0, 106.1, 98.9, 46.8, 29.4, 24.0, 22.7, 21.0, 17.8, 14.6. HRMS (ESI) calcd for $C_{19}H_{26}N_2O$ ($[M+H]^+$) 299.2117; found: 299.2115.

***N*-(1-Adamantyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (13).** Yield 65% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.21 (s, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 6.65 (s, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 2.09 (s, 6H), 2.07 (br s, 3H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.1, 136.9, 132.8, 131.8, 130.3, 125.7, 122.0, 109.8, 101.9, 51.9, 41.6, 36.5, 29.3, 21.9, 18.9. HRMS (ESI) calcd for $C_{21}H_{26}N_2O$ ($[M+H]^+$) 323.2117; found: 323.2105.

***N*-(2-Adamantyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (14).** Purified by re-crystallization from EtOH-Et_2O. Yield 82% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.30 (s, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.02 (s, 1H), 6.66 (s, 1H), 4.09 (d, J = 5.2 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 2.14 (d, J = 12.4 Hz, 2H), 1.98 (s, 2H), 1.86–1.83 (m, 6H), 1.73 (s, 2H), 1.54 (d, J = 12.0 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.8, 136.7, 132.6, 130.5, 130.0, 125.3, 121.6, 109.4, 102.2, 53.6, 37.2, 36.9, 31.4, 31.1, 26.8, 21.5, 18.4. HRMS (ESI) calcd for $C_{21}H_{26}N_2O$ ($[M+H]^+$) 323.2117; found: 323.2113.

***N*-(Cyclohexylmethyl)-4,6-dimethyl-1*H*-indole-2-carboxamide (15).** Yield 80% (white powder). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.07 (s, 1H), 6.82 (d, J = 8.9 Hz, 2H), 6.26 (m, 1H), 3.36 (t, J = 6.5 Hz, 2H), 2.53 (s, 3H), 2.44 (s, 3H), 1.85–1.62 (m, 6H), 1.30–1.21 (m, 3H), 1.08–1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 136.2, 134.2, 130.5, 129.3, 125.3, 122.4, 108.8, 99.7, 45.4, 37.8, 30.5, 26.0, 25.4, 21.4, 18.2. HRMS (ESI) calcd for $C_{18}H_{24}N_2O$ ($[M+H]^+$) 285.1889; found: 285.1967.

***N*-Cyclohexyl-*N*,4,6-trimethyl-*1H*-indole-2-carboxamide (16).** Yield 88% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.33 (s, 1H), 7.05 (s, 1H), 6.74-6.67 (m, 2H), 4.33 (m, 1H), 3.07 (br s, 3H), 2.45 (s, 3H), 2.35 (s, 3H), 1.81-1.56 (m, 7H), 1.34-1.31 (m, 2H), 1.18-1.10 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 162.6, 136.0, 132.5, 129.9, 129.4, 125.1, 121.7, 109.2, 29.6, 25.3, 24.9, 21.5, 18.3. HRMS (ESI) calcd for $C_{18}H_{24}N_2O$ ($[M+H]^+$) 285.1961; found: 285.1969.

(4,6-Dimethyl-*1H*-indol-2-yl)(piperidin-1-yl)methanone (17). Recrystallization from EtOH-Et_2O. Yield 93% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.32 (s, 1H), 7.01 (s, 1H), 6.68 (d, J = 1.2 Hz, 1H), 6.66 (s, 1H), 3.71 (br s, 4H), 2.43 (s, 3H), 2.34 (s, 3H), 1.66–1.64 (m, 2H), 1.57–1.56 (m, 4H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 162.5, 136.5, 132.8, 130.3, 129.5,

125.4, 122.1, 109.6, 102.5, 26.3, 24.6, 21.9, 18.8. HRMS (ESI) calcd for $C_{16}H_{20}N_2O$ ($[M+H]^+$) 257.1648; found: 257.1652.

***N*-Cyclohexyl-1,4,6-trimethyl-*1H*-indole-2-carboxamide (18).** Yield 74% (white powder). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.06 (d, J = 7.6 Hz, 1H), 4.02 (s, 3H), 3.99–3.93 (m, 1H), 2.52 (s, 3H), 2.48 (s, 3H), 2.08–2.05 (m, 2H), 1.82–1.66 (m, 3H), 1.51–1.40 (m, 2H), 1.33–1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 138.9, 133.8, 130.9, 130.4, 123.6, 122.2, 107.1, 101.4, 47.9, 32.9, 31.2, 25.2, 24.6, 21.7, 18.1. HRMS (ESI) calcd for $C_{18}H_{24}N_2O$ ($[M+H]^+$) 285.1889; found: 285.1974.

***N*-Cycloheptyl-4,6-dimethylbenzofuran-2-carboxamide (19).** Purified by flash chromatography (CH_2Cl_2, 100%). Yield 83% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.39 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.23 (s, 1H), 6.94 (s, 1H), 3.96 (m, 1H), 2.46 (s, 3H), 2.40 (s, 3H), 1.86–1.82 (m, 2H), 1.65–1.41 (m, 10H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.1, 154.5, 148.4, 136.6, 131.7, 125.2, 124.7, 109.0, 107.9, 50.1, 34.2, 27.7, 23.9, 21.4, 18.1. HRMS (ESI) calcd for $C_{18}H_{23}NO_2$ ($[M+H]^+$) 286.1802; found: 286.1813.

***N*-Cyclooctyl-4,6-dimethylbenzofuran-2-carboxamide (20).** Purified by flash chromatography (CH_2Cl_2/CH_3OH, 9:1). Yield 69% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.37 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.24 (s, 1H), 6.95 (s, 1H), 4.02 (m, 1H), 2.46 (s, 3H), 2.40 (s, 3H), 1.72–1.69 (m, 6H), 1.62–1.50 (m, 8H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.1, 154.5, 148.4, 136.6, 131.7, 125.2, 124.7, 109.0, 107.9, 48.9, 31.6, 26.8, 25.1, 23.5, 21.4, 18.1. HRMS (ESI) calcd for $C_{19}H_{25}NO_2$ ($[M+Na]^+$) 322.1778; found: 322.1786.

***N*-(1-Adamantyl)-4,6-dimethylbenzofuran-2-carboxamide (21).** Purified by flash chromatography (CH_2Cl_2/CH_3OH, 9:1). Yield 72% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.57 (s, 1H), 7.54 (s, 1H), 7.23 (s, 1H), 6.94 (s, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 2.08

(br s, 9H), 1.66 (m, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.6, 154.4, 148.5, 136.5, 131.7, 125.2, 124.7, 109.0, 107.8, 51.7, 40.8, 36.0, 28.8, 21.4, 18.1. HRMS (ESI) calcd for $C_{21}H_{25}NO_2$ ($[M+H]^+$) 324.1958; found: 324.1966.

***N*-(bicyclo[2.2.1]-2-heptanyl)-4,6-dimethylbenzofuran-2-carboxamide (22).** Purified by flash chromatography (CH_2Cl_2, 100 %). Yield 82% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.24 (d, J = 6.7 Hz, 1H), 7.59 (s, 1H), 7.24 (s, 1H), 6.94 (s, 1H), 3.72 (m, 1H), 2.46 (s, 3H), 2.40 (s, 3H), 2.24 (s, 1H), 2.18 (d, J = 2.4 Hz, 1H), 1.66–1.40 (m, 5H), 1.22–1.09 (m, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.7, 154.5, 148.2, 136.6, 131.7, 125.2, 124.7, 109.0, 108.0, 52.6, 42.0, 37.9, 35.2, 34.9, 28.0, 26.3, 21.4, 18.1. HRMS (ESI) calcd for $C_{18}H_{21}NO_2$ ($[M+H]^+$) 284.1645; found: 284.1644.

***N*-Hexyl-4,6-dimethylbenzofuran-2-carboxamide (23).** Purified by flash chromatography (CH_2Cl_2/CH_3OH, 9:1). Yield 74% (pale yellow solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.57 (t, J = 5.6 Hz, 1H), 7.51 (s, 1H), 7.23 (s, 1H), 6.95 (s, 1H), 3.24 (m, 2H), 2.46 (s, 3H), 2.40 (s, 3H), 1.53–1.48 (m, 2H), 1.27 (br s, 6H), 0.86 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.1, 154.5, 148.3, 136.7, 131.8, 125.3, 124.7, 109.0, 107.9, 38.6, 31.0, 29.0, 26.1, 22.0, 21.3, 18.1, 13.9. HRMS (ESI) calcd for $C_{17}H_{23}NO_2$ ($[M+H]^+$) 274.1802; found: 274.1805.

5-Chloro-*N*-cyclooctylbenzofuran-2-carboxamide (24). Purified by flash chromatography (100% CH_2Cl_2). Yield 79% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.57 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.47 (ddd, J = 8.8, 2.1, 0.8 Hz, 1H), 4.04–3.98 (m, 1H), 1.75–1.65 (m, 6H), 1.60–1.45 (m, 8H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 156.5, 152.6, 150.8, 128.8, 127.9, 126.5, 122.0, 113.4, 108.6, 49.1, 31.6 (2C), 26.7 (2C), 25.1, 23.5 (2C). HRMS (ESI) calcd for $C_{17}H_{20}ClNO_2$ ($[M+H]^+$) 306.1255; found: 306.1252.

5-Chloro-*N*-(1-adamantyl)benzofuran-2-carboxamide (25). Purified by re-crystallization from CH_3OH. Yield 84% (off-white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.51 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 2.07 (br s, 9H), 1.65 (m, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.0, 152.5, 151.0, 128.8, 127.9, 126.5, 121.9, 113.4, 108.5, 51.9, 40.7, 35.9, 28.8. HRMS (ESI) calcd for $C_{19}H_{20}ClNO_2$ ([M+H]+) 330.1255; found: 330.1264.

***N*-Cyclohexyl-1*H*-indole-2-carboxamide (26)**. Yield 95% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.51 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.18–7.14 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 3.79 (br s, 1H), 1.85–1.59 (m, 5H), 1.38–1.27 (m, 4H), 1.15–1.13 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2, 136.4, 132.1, 127.1, 123.2, 121.4, 119.7, 112.3, 102.5, 48.0, 32.6, 25.3, 25.0. HRMS (ESI) calcd for $C_{15}H_{18}N_2O$ ($[M+H]^+$) 243.1491; found: 243.1498.

***N*-(3-Fluoro-4-methylphenyl)-1*H*-indole-2-carboxamide (27).** Yield 83% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.75 (s, 1H), 10.30 (s, 1H), 7.73 (d, J = 12.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.41 (s, 1H), 7.27–7.21 (m, 2H), 7.07 (t, J = 8.0 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.5 (d, J = 239 Hz), 159.8, 138.4 (d, J = 11 Hz), 136.9, 131.5 (d, J = 6 Hz), 131.3, 127.0, 124.0, 121.9, 120.1, 118.9 (d, J = 17 Hz), 115.7 (d, J = 3 Hz), 112.5, 106.9 (d, J = 27 Hz), 104.1, 13.7 (d, J = 3 Hz). HRMS (ESI) calcd for $C_{16}H_{13}FN_2O$ ($[M+H]^+$) 269.1085; found: 269.1087.

***N*-Cycloheptyl-4,6-difluoro-1*H*-indole-2-carboxamide (28).** Yield 68 % (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.93, 8.33 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.03 (d, J = 8.8 Hz), 6.87 (t, J = 10.4 Hz, 1H), 3.98 (m, 1H), 1.89-1.85 (m, 2H), 1.65-1.42 (m, 10H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2 (d, J = 236 Hz), 159.0, 157.0 (d, J = 246 Hz), 137.5 (t, J = 15.1 Hz),

133.0, 113.2 (d, J = 22 Hz), 98.2, 95.3 (d, J = 23 Hz), 94.7 (d, J = 26 Hz), 50.1, 34.3, 27.9, 23.8. HRMS (ESI) calcd for $C_{16}H_{18}F_2N_2O$ ($[M+H]^+$) 293.1460; found: 293.1472

***N*-Cyclooctyl-4,6-difluoro-1*H*-indole-2-carboxamide (29).** Yield 69 % (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.93, 8.31 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.03 (d, J = 9.6 Hz), 6.87 (t, J = 10.4 Hz, 1H), 4.04-4.00 (m, 1H), 1.80-1.64 (m, 6H), 1.60-1.50 (m, 8H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2 (d, J = 237 Hz), 159.0, 157.0 (d, J = 247 Hz), 137.5 (t, J = 14.9 Hz), 133.1, 113.1 (d, J = 22 Hz), 98.2, 95.3 (d, J = 23 Hz), 94.7 (d, J = 26 Hz), 49.0, 31.5, 26.9, 25.0, 23.4. HRMS (ESI) calcd for $C_{17}H_{20}F_2N_2O$ ($[M+H]^+$) 307.1617; found: 307.1626.

***N*-(1-Adamantyl)-6-methoxy-1*H*-indole-2-carboxamide (30).** Purified by flash chromatography (EtOAc–hexane 1:3 to 3:2) followed by recrystallization from CH_3OH. Yield 77% (pale yellow powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.23 (s, 1H), 7.46–7.42 (m, 2H), 7.08 (d, J = 1.8 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 6.67 (dd, J = 8.7, 2.2 Hz, 1H), 3.76 (s, 3H), 2.09–2.06 (m, 9H), 1.67 (br s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.5, 156.8, 137.2, 131.5, 122.1, 121.3, 110.7, 103.0, 94.1, 55.0, 51.4, 41.1, 36.1, 28.9. HRMS (ESI) calcd for $C_{20}H_{24}N_2O_2$ ($[M+H]^+$) 325.1911; found: 325.1910.

***N*-(1-Adamantyl)-5-chloro-1*H*-indole-2-carboxamide (31).** Purified by flash chromatography (EtOAc–hexane 1:3 to 1:1) followed by re-crystallization from CH_3OH. Yield 40% (pale yellow powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.63 (s, 1H), 7.65 (br s, 2H), 7.42 (d, J = 8.7 Hz, 1H), 7.17–7.14 (m, 2H), 2.09–2.06 (m, 9H), 1.66 (br s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.1, 134.6, 134.2, 128.1, 124.0, 123.1, 120.4, 113.7, 102.3, 51.7, 41.0, 36.0, 28.9. HRMS (ESI) calcd for $C_{19}H_{21}ClN_2O$ ($[M+H]^+$) 329.1415; found: 329.1399.

***N*-(1-Adamantyl)-6-hydroxy-1*H*-indole-2-carboxamide (32).** Compound **30** (0.73 mmol) was dissolved in anhydrous CH_2Cl_2 (7 mL) and cooled to –78 °C. Subsequently BBr_3 (1.0 M

solution in CH_2Cl_2, 4.4 mL, 6.0 equiv) was added dropwise and the reaction mixture was allowed to warm gradually to room temperature within 1 h. Stirring was continued at the same temperature an additional 3 h. The reaction was quenched with water and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (EtOAc–hexane 1:3 to 1:1) followed by preparative HPLC. Yield 52% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.00 (s, 1H), 9.11 (s, 1H), 7.35–7.33 (m, 2H), 7.01 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.55 (dd, J = 8.6, 2.1 Hz, 1H), 2.07 (br s, 9H), 1.66 (br s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.6, 154.6, 137.6, 131.0, 121.9, 120.6, 111.0, 103.1, 96.4, 51.4, 41.1, 36.1, 28.9. HRMS (ESI) calcd for $C_{19}H_{22}N_2O_2$ ($[M+H]^+$) 311.1754; found: 311.1767.

***N*-Cyclooctyl-6-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxamide (33).** Yield 80% (white solid). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.67 (s, 1H), 8.39 (br s, 2H), 7.04 (s, 1H), 6.91 (s, 1H), 4.09–3.99 (m, 1H), 3.83 (s, 3H), 1.80–1.48 (m, 14H); ^{13}C NMR (400 MHz, d_6-DMSO) δ 159.3, 157.4, 137.3, 135.7, 131.7, 130.7, 100.4, 97.5, 53.6, 49.2, 31.6, 26.9, 25.1, 23.5. HRMS (ESI) calcd for $C_{17}H_{23}N_3O_2$ ($[M+H]^+$) 302.1863; found: 302.1874.

***N*-(1-Adamantyl)-6-methoxy-1*H*-pyrrolo[3,2-*c*]pyridine-2-carboxamide (34)**. Yield 70% (white solid).^{1}H NMR (400 MHz, d_6-DMSO) δ 11.60 (s, 1H), 8.39 (s, 1H), 7.75 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 3.83 (s, 3H), 2.09 (br s, 9H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.9, 157.4, 137.9, 135.7, 131.6, 130.6, 100.7, 97.5, 53.6, 51.9, 41.0, 36.1, 28.9. HRMS (ESI) calcd for $C_{19}H_{23}N_3O_2$ ($[M+H]^+$) 326.1863; found: 326.1867.

***N*-Cycloheptyl-4,6-bis(trifluoromethyl)-1*H*-indole-2-carboxamide (35).** Yield 54 % (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.59 (s, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.66 (s, 1H), 7.54 (s, 1H), 4.04 (m, 1H), 1.93-1.87 (m, 2H), 1.71-1.55 (m, 10H); ^{13}C NMR (100

MHz, d_6-DMSO) δ 158.5, 137.0, 135.7, 125.6 (d, J = 21 Hz), 125.3, 122.9 (d, J = 21 Hz), 122.8 (q, J = 32 Hz), 122.0 (q, J = 33 Hz), 114.1, 113.4, 100.4, 50.3, 34.3, 27.9, 23.8. HRMS (ESI) calcd for $C_{18}H_{18}F_6N_2O$ ($[M+H]^+$) 393.1396; found: 393.1386.

***N*-Cyclooctyl-4,6-bis(trifluoromethyl)-1*H*-indole-2-carboxamide (36).** Yield 61 % (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.58 (s, 1H), 8.67 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 4.07 (m, 1H), 1.82-1.51 (m, 14H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.5, 137.0, 135.7, 125.7 (d, J = 20 Hz), 125.3, 123.0 (d, J = 21 Hz), 122.8 (q, J = 32 Hz), 122.0 (q, J = 33 Hz), 114.0, 113.4, 100.4, 49.3, 31.4, 26.8, 25.0, 23.4. HRMS (ESI) calcd for $C_{19}H_{20}F_6N_2O$ ($[M+H]^+$) 407.1553; found:407.1562.

***N*-Cycloheptyl-4,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxamide (37).** Yield 36% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.83 (s, 1H), 7.24 (s, 1H), 7.00 (s, 1H), 4.04–4.00 (m, 1H), 2.55 (s, 3H), 2.40 (s, 3H), 1.91–1.87 (m, 2H), 1.72–1.42 (m, 10H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 153.7, 142.3, 136.0, 132.8, 131.4, 127.9, 125.4, 111.3, 51.0, 33.8, 27.9, 23.6, 21.2, 16.7. HRMS (ESI) calcd for $C_{17}H_{23}N_3O$ ($[M+H]^+$) 286.1914; found: 286.1921.

***N*-Cyclooctyl-4,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxamide (38).** Yield 51% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.33 (s, 1H), 7.29 (s, 1H), 7.10 (s, 1H), 4.12–4.04 (m, 1H), 2.58 (s, 3H), 2.42 (s, 3H), 1.81–1.72 (m, 6H), 1.63–1.54 (m, 8H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 154.3, 142.8, 135.4, 133.6, 132.5, 127.4, 125.5, 111.5, 49.9, 31.0, 26.8, 24.9, 23.3, 21.2, 16.7. HRMS (ESI) calcd for $C_{18}H_{25}N_3O$ ($[M+H]^+$) 300.2070; found: 300.2080.

***N*-(1-Adamantyl)-4,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxamide (39).** Yield 40% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.94 (s, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 2.52 (s, 3H), 2.39 (s, 3H), 2.11–2.09 (br s, 9H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ

156.3, 144.3, 135.6, 134.9, 134.0, 126.2, 126.0, 111.7, 52.0, 40.7, 35.8, 28.9, 21.2, 16.6. HRMS (ESI) calcd for $C_{20}H_{25}N_3O$ ($[M+H]^+$) 324.2070; found: 324.2077.

***N*-(2-Adamantyl)-4,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxamide (40).** Yield 44% (white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.12 (d, J = 7.2 Hz, 1H), 7.23 (s, 1H), 6.96 (s, 1H), 4.11 (d, J = 7.6 Hz, 1H), 2.53 (s, 3H), 2.39 (s, 3H), 2.02 (s, 2H), 1.99 (d, J = 13.2 Hz, 2H), 1.86 (br s, 6H), 1.74 (s, 2H), 1.65 (d, J = 12.4 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.2, 144.2, 136.6, 135.9, 133.5, 126.2, 125.8, 112.1, 53.4, 36.9, 36.5, 31.2, 26.6, 21.2, 16.6. HRMS (ESI) calcd for $C_{20}H_{25}N_3O$ ($[M+H]^+$) 324.2070; found: 324.2076.

***N*-Cycloheptyl-4,6-dimethyl-1*H*-indole-3-carboxamide (41).** Yield 44 % (off-white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.17 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.00 (s, 1H), 6.65 (s, 1H), 3.94 (m, 1H), 2.53 (s, 3H), 2.33 (s, 3H), 1.90–1.86 (m, 2H), 1.68–1.56 (m, 10H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 164.5, 136.8, 130.7, 130.1, 126.2, 123.2, 122.3, 113.6, 109.0, 50.0, 34.4, 27.8, 24.0, 21.1, 21.0. HRMS (ESI) calcd for $C_{18}H_{24}N_2O$ ($[M+H]^+$) 285.1961; found: 285.1973.

***N*-Cyclooctyl-4,6-dimethyl-1*H*-indole-3-carboxamide (42).** Yield 34 % (off-white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.17 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 6.99 (s, 1H), 6.65 (s, 1H), 3.96 (m, 1H), 2.53 (s, 3H), 2.33 (s, 3H), 1.77–1.49 (m, 14H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 164.4, 136.7, 130.7, 130.1, 126.2, 123.2, 122.3, 113.7, 109.0, 48.7, 31.7, 26.9, 25.1, 23.6, 21.1, 20.9. HRMS (ESI) calcd for $C_{19}H_{26}N_2O$ ($[M+H]^+$) 299.2118; found: 299.2119.

***N*-(1-Adamantyl)-4,6-dimethyl-1*H*-indole-3-carboxamide (43).** Yield 38 % (off-white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.11 (s, 1H), 7.47 (d, J = 2.8 Hz, 1H), 7.26 (s, 1H), 6.98 (s, 1H), 6.64 (s, 1H), 2.52 (s, 3H), 2.33 (s, 3H), 2.07–2.05 (m, 9H), 1.66 (s, 6H); ^{13}C NMR

(100 MHz, d_6-DMSO) δ. 165.5, 136.6, 130.6, 130.0, 125.9, 123.1, 122.3, 114.7, 109.0, 51.0, 41.1, 36.2, 28.9, 21.1, 20.8. HRMS (ESI) calcd for $C_{21}H_{26}N_2O$ ($[M+H]^+$), 323.2118; found: 323.2109

***N*-(2-Adamantyl)-4,6-dimethyl-1*H*-indole-3-carboxamide (44).** Yield 42 % (off-white powder). ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.21 (s, 1H), 7.65 (d, J = 6.8 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.01 (s, 1H), 6.65 (s, 1H), 4.03 (m, 1H), 2.52 (s, 3H), 2.34 (s, 3H), 2.14 (d, J = 12.8 Hz, 2H), 1.96 (s, 2H), 1.85–1.79 (m, 6H), 1.72 (s, 2H), 1.53 (d, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.3, 136.8, 130.7, 130.1, 126.7, 123.2, 122.4, 113.4, 109.1, 53.4, 37.3, 37.0, 31.4, 31.1, 26.9, 21.1, 20.8. HRMS (ESI) calcd for $C_{21}H_{26}N_2O$ ($[M+H]^+$) 323.2118; found: 323.2110.

Biology. MIC was determined by using MABA as reported previously.[22,23] Cytotoxicity was evaluated on Vero cells also by using MABA format.[22] Oral bioavalability was analyzed by using serum inhibition titration assay.[31] Briefly, compounds were ground to homogenate suspension in 0.5% carboxymethyl cellulose. Six-week old female BALB/c mice were single-dosed at 300 or 100 mg/kg by oral gavage. Isoniazid at 10 mg/kg was used as positive control and 0.5% carboxymethyl cellulose treatment was used as vehicle control. At 15, 30 and 60 min after administration, cardiac blood was collected and serum was separated. Two-fold serial titration was carried out using 96-well plates, 10^4 colony forming units of *M. tuberculosis* H37Rv were added to testing wells. Plates were then incubated and processed as regular MABA.

ASSOCIATED CONTENT

Supporting Information.

Experimental details for synthesis of all intermediates and a chart of purity for all target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*To whom correspondence should be addressed. E-mail: wbishai1@jhmi.edu (biological screening) and kozikowa@uic.edu [medicinal chemistry].

Present Addresses

^Current address: Dipartimento Farmaceutico, Via G.P. Usberti 27/a, University of Parma, Parma, 43121, Italy.

§Current address: Merrimack Pharmaceuticals, 1 Kendall Square, Suite B7201, Cambridge, Massachusetts, 02139-1670, United States.

⊥Current address: College of Pharmacy, Chicago State University, 9501 S. King Drive, Chicago, Illinois, 60628-1598, United States.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Prof. P. Moodley, W. R. Jacobs, Jr., and M. Larsen for generously sharing clinical isolates of *M. tuberculosis* from KwaZulu-Natal and for providing their drug susceptibility phenotypes. Dr S. C. Cho and Prof. S. G. Franzblau are acknowledged for the phenotypic high-throughput screening of the ASDI library. The authors thank K-RITH for their financial support of this project.

ABBREVIATIONS

SAR, structure–activity relationship; MABA, microplate Alamar Blue assay; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; MIC, minimum inhibitory concentration; TFA, trifluoroacetic acid; *M. tuberculosis*, *Mycobacterium tuberculosis*.

REFERENCES

(1) World Health Organisation, Tuberculosis: http://www.who.int/mediacentre/factsheets/fs104/en/index.html (accessed February 11, 2013).

(2) WHO Global Tuberculosis Report 2012, http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf (accessed January 8, 2013).

(3) Ying, Z. The magic bullets and tuberculosis drug targets. *Annu. Rev. Pharmacol. Toxicol.* **2005**, 529-564.

(4) Ormerod, L. P. Directly observed therapy (DOT) for tuberculosis: why, when, how and if? *Thorax* **1999**, *54*, S42-S45.

(5) Jassal, M. S.; Bishai, W. R. Epidemiology and Challenges to the Elimination of Global Tuberculosis. *Clin. Infect. Dis.* **2010**, *50*, S156-S164.

(6) Koul, A.; Arnoult, E.; Lounis, N.; Guillemont, J.; Andries, K. The challenge of new drug discovery for tuberculosis. *Nature* **2011**, *469*, 483-490.

(7) Working Group on New TB Drugs, http://www.newtbdrugs.org/pipeline.php (accessed January 25, 2013).

(8) Lienhardt, C.; Vernon, A.; Raviglione, M. C. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. *Curr. Opin. Pulmon. Med.* **2010**, *16*, 186-193.

(9) Ma, Z.; Lienhardt, C.; McIlleron, H.; Nunn, A. J.; Wang, X. Global tuberculosis drug development pipeline: the need and the reality. *Lancet* **2010**, *375*, 2100-2109.

(10) Andries, K.; Verhasselt, P.; Guillemont, J.; Gohlmann, H. W. H.; Neefs, J. M.; Winkler, H.; Van Gestel, J.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. *Science* **2005**, *307*, 223-227.

(11) Lenaerts, A. J.; Gruppo, V.; Marietta, K. S.; Johnson, C. M.; Driscoll, D. K.; Tompkins, N. M.; Rose, J. D.; Reynolds, R. C.; Orme, I. M. Preclinical testing of the nitroimidazopyran PA-824 for activity against Mycobacterium tuberculosis in a series of in vitro and in vivo models. *Antimicrob. Agents Chemother.* **2005**, *49*, 2294-2301.

(12) Schecter, G. F.; Scott, C.; True, L.; Raftery, A.; Flood, J.; Mase, S. Linezolid in the Treatment of Multidrug-Resistant Tuberculosis. *Clin. Infect. Dis.* **2010**, *50*, 49-55.

(13) Shandil, R. K.; Jayaram, R.; Kaur, P.; Gaonkar, S.; Suresh, B. L.; Mahesh, B. N.; Jayashree, R.; Nandi, V.; Bharath, S.; Balasubramanian, V. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against Mycobacterium tuberculosis: Evaluation of in vitro and

pharmacodynamic indices that best predict in vivo efficacy. *Antimicrob. Agents Chemother.* **2007**, *51*, 576-582.

(14) Rosenthal, I. M.; Zhang, M.; Williams, K. N.; Peloquin, C. A.; Tyagi, S.; Vernon, A. A.; Bishai, W. R.; Chaisson, R. E.; Grosset, J. H.; Nuermberger, E. L. Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model. *Plos Medicine* **2007**, *4*, 1931-1939.

(15) United States Food and Drug Administration, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm (accessed January 14, 2013).

(16) Mao, J.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. HTS, chemical hybridization, and drug design identify a chemically unique antituberculosis agent-coupling serendipity and rational approaches to drug discovery. *ChemMedChem* **2007**, *2*, 811-813.

(17) Mao, J.; Wang, Y.; Wan, B.; Kozikowski, A. P.; Franzblau, S. G. Design, synthesis, and pharmacological evaluation of mefloquine-based ligands as novel antituberculosis agents. *ChemMedChem* **2007**, *2*, 1624-1630.

(18) Pieroni, M.; Lilienkampf, A.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. Synthesis, Biological Evaluation, and Structure-Activity Relationships for 5-[(*E*)-2-Arylethenyl]-3-isoxazolecarboxylic Acid Alkyl Ester Derivatives as Valuable Antitubercular Chemotypes. *J. Med. Chem.* **2009**, *52*, 6287-6296.

(19) Lilienkampf, A.; Mao, J.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. Structure-Activity Relationships for a Series of Quinoline-Based Compounds Active against

Replicating and Nonreplicating Mycobacterium tuberculosis. *J. Med. Chem.* **2009**, *52*, 2109-2118.

(20) Lilienkampf, A.; Pieroni, M.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. Rational Design of 5-Phenyl-3-isoxazolecarboxylic Acid Ethyl Esters as Growth Inhibitors of Mycobacterium tuberculosis. A Potent and Selective Series for Further Drug Development. *J. Med. Chem.* **2010**, *53*, 678-688.

(21) Pieroni, M.; Lilienkampf, A.; Wang, Y.; Wan, B.; Cho, S.; Franzblau, S. G.; Kozikowski, A. P. NOC Chemistry for Tuberculosis-Further Investigations on the Structure-Activity Relationships of Antitubercular Isoxazole-3-carboxylic Acid Ester Derivatives. *ChemMedChem* **2010**, *5*, 1667-1672.

(22) Pieroni, M.; Tipparaju, S. K.; Lun, S.; Song, Y.; Sturm, A. W.; Bishai, W. R.; Kozikowski, A. P. Pyrido[1,2-a]benzimidazole-Based Agents Active Against Tuberculosis (TB), Multidrug-Resistant (MDR) TB and Extensively Drug-Resistant (XDR) TB. *ChemMedChem* **2011**, *6*, 334-342.

(23) Collins, L. A.; Franzblau, S. G. Microplate Alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004-1009.

(24) Lun, S.; Guo, H.; Onajole, O. K.; Pieroni, M.; Gunosewoyo, H. Chen, G.; Tipparaju, S. K.; Ammerman, N. C.; Kozikowski, A. P.; Bishai, W. R. Identification of a new molecular class active against Mycobacterium tuberculosis (unpublished results).

(25) Kurdukar, R.; Subba Rao, N. V. Physiologically active compounds. VII. Synthesis of halo and nitro coumarones. *Proc. Indian Acad. Sci. Section A* **1963**, *58*, 336-342.

(26) Dean, F. M.; Halewood, P.; Mongkolsuk, S.; Robertson, A.; Whalley, W. B. Usnic Acid. Part IX. A revised Structure for Usnolic Acid and the Resolution of Usnic Acid. *J. Chem. Soc.* **1953**, 1250-1261.

(27) Suzuki, T.; Horaguchi, T.; Shimizu, T.; Abe, T. Benzofuran Derivatives .1. On the Effects of Substituents in Benzofuran Syntheses. *Bull. Chem. Soc. Jpn* **1983**, *56*, 2762-2767.

(28) Li, J. C.; Rush, T. S.; Li, W.; DeVincentis, D.; Du, X. M.; Hu, Y. H.; Thomason, J. R.; Xiang, J. S.; Skotnicki, J. S.; Tam, S.; Cunningham, K. M.; Chockalingam, P. S.; Morris, E. A.; Levin, J. I. Synthesis and SAR of highly selective MMP-13 inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4961-4966.

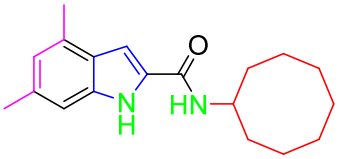
(29) Ballell, L.; Bates, R. H.; Young, R. J.; Alvarez-Gomez, D.; Alvarez-Ruiz, E. Barroso, V.; Blanco, D.; Crespo, B.; Escribano, J.; Gonzalez, R.; Lozano, S.; Huss, S.; Santos-Villarejo, A.; Julio Martin-Plaza, J.; Mendoza, A.; Jose Rebollo-Lopez, M.; Remuinan-Blanco, M.; Luis Lavandera, J.; Perez-Herran, E.; Javier Gamo-Benito, F.; Francisco Garcia-Bustos, J.; Barros, D.; Castro, J. P.; Cammack, N. Fueling Open-Source Drug Discovery: 177 Small-Molecule Leads against Tuberculosis. *ChemMedChem* **2013**, 8, 313-321.

(30) Ioerger, T. R.; Koo, S.; No, E.-G.; Chen, X.; Larsen, M. H.; Jacobs, W. R., Jr.; Pillay, M.; Sturm, A. W.; Sacchettini, J. C. Genome Analysis of Multi- and Extensively-Drug-Resistant Tuberculosis from KwaZulu-Natal, South Africa. *Plos One* **2009**, *4,* e7778.

(31) Chopra, S.; Matsuyama, K.; Tran, T.; Malerich, J. P.; Wan, B.; Franzblau, S. G.; Lun, S.; Guo, H.; Maiga, M. C.; Bishai, W. R.; Madrid, P. B. Evaluation of gyrase B as a drug target in Mycobacterium tuberculosis. *J. Antimicrob. Chemother.* **2012**, *67*, 415-421.

(32) Peterson, L. R.; Shanholtzer, C. J. Tests for Bactericidal Effects of Antimicrobial Agents - Technical Performance and Clinical Relevance. *Clin. Microbiol. Rev.* **1992**, 5, 420-432.

TABLE OF CONTENTS GRAPHICS



Indole-2-carboxamide 12

MIC (H_{37}Rv) = 0.013 μM

Vero cell IC_{50} = 54 μM

Selectivity index = 4,100

Active against XDR-TB strains

Orally bioactive in serum inhibition titration (SIT) assay