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Research Article

Copper- and Ligand-Free Sonogashira Cross-Coupling: Access to Novel 3-Aminoindole Derivatives and Their Biological Evaluations

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Indole-containing compounds are widely distributed in the plant and animal kingdom, and their biological activity and pharmacological properties have prompted research into their chemical properties. This study developed a one-pot methodology for the synthesis of 3-aminoindole derivatives using copper- and ligand-free Sonogashira cross-coupling reaction conditions. The synthesised 3-aminoindole derivatives were confirmed using spectroscopic techniques. The resulting 3-aminoindole derivatives were biologically evaluated against *Mycobacterium tuberculosis* and *Plasmodium falciparum*. For example, indole derivatives **10a** (7.813 μM) and **10j** (8.332 μM) were the most active derivatives in the CAS and ADC media, respectively.

1. Introduction

Bicyclic heterocyclic structures are widespread in a wide range of biologically essential compounds, including indoles. Indole, also known as benzopyrrole, is an organic chemical molecule with a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring, and it has been identified as a crucial component in medicinal chemistry [1]. Indole scaffolds have been discovered in various synthesised pharmacological compounds and exhibit numerous biological activities. Over 10000 biologically active indole derivatives have been identified to date, of which over 200 are currently marketed as drugs or are undergoing clinical trials [2]. Indoles form an important part of heterocyclic compounds and are found in naturally occurring nitrogen-containing heterocycles that are widely distributed in plant kingdoms [3, 4]. The indole nucleus is an abundant feature of alkaloids and represents a privileged structural motif for pharmaceutically active compounds [5–7].

3-Amido- and 3-amino-substituted indoles are among the several known indole derivatives that have received little attention. Synthetic 3-aminoindoles derivatives are known to be exceptional kinase inhibitors and valuable for treating overactive proliferative disorders, infections related to angiogenesis, inflammation and neurodegeneration, depressive disorders, and anxiety [8]. For example, Chen et al. developed a sequence of 3-amidoindole hybrids which displayed good activity against human breast cancer cell lines (T47D, BT549, and MDA-MB-231) with IC_{50} values of 0.04 to 6.43 μM (compound **1**, Figure 1) [9, 10]. In addition to Chen et al., Daly et al. created some new indole cores containing azo functional groups, and the compounds showed activity against methicillin-resistant *Staphylococcus aureus* (MRSA). In comparison to vancomycin with an MIC_{50} value of 2.80 μg/mL, the synthetic analogues were

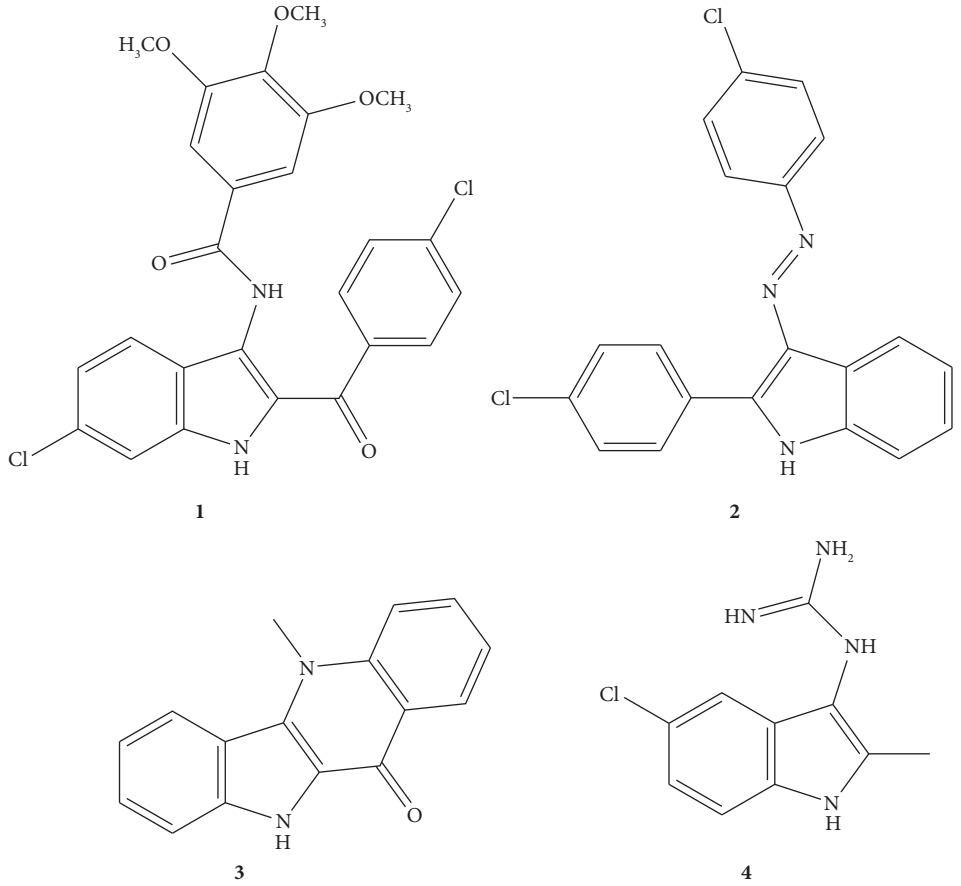
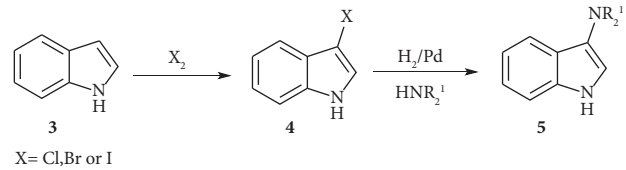


Figure 1: Biologically active 3-aminoindole derivatives.

more active. Among them, compound **2** (Figure 1) ($MIC_{50} = 0.6$ mg/mL) was the most potent against MRSA [11]. Moreover, 3-aminoindole derivative **3** was seen as a potential treatment for type 2 diabetes [12], while fused 3-aminoindole **4** possessed excellent antiplasmodial activity (Figure 1) [13].

Until recently, 3-aminoindoles have been synthesised using multistep procedures that frequently included indole nitrogen protection and deprotection phases. In general, the heterocycle is made by reacting *N*-nucleophiles such as 2-aminobenzonitrile or substituted phenylhydrazines with suitable carbonyl compounds (Fischer indole synthesis) [14]. The development of appropriate synthetic techniques for accessing these indole analogues has received a lot of attention, and a few more diverse and efficient methodologies for their synthesis have recently been devised [15]. For instance, Naoki et al. developed a Buchwald–Hartwig amination (Scheme 1) which addressed the difficulties in controlling the reactivity and regioselectivity of the indole nucleus. The reaction yield ranged from 74% to 83%. Unfortunately, this method required a halogen functionalized indole in the presence of a palladium catalyst for amination to take place [16–20].

In an effort to avoid the halogenation of indoles and improve access to 3-aminoindoles, Ortiz et al. developed an indole position 3 selective amidation method using *N*-[(benzenesulfonyl)oxy]amides in the presence of zinc



Scheme 1: Buchwald–Harting amination reaction.

chloride. While this method takes advantage of the reactivity of indole nucleus, *N*-[(benzenesulfonyl)oxy]amides are not readily available reagents [21]. In addition, several non-palladium catalyst methods have been developed to access 3-aminoindoles. For example, Seong and co-workers developed an efficient base-mediated synthetic method to access 3-aminoindoles from benzonitriles [22], Hu and co-investigators used a rhodium-based catalyst for the electrophilic amidation of 2-alkynylanilines for the synthesis of 3-amidoindoles [23], while Matsuda et al. reported on copper-catalysed annulative electrophilic amination of 2-alkynylanilines to access 3-aminonindoles (Scheme 2) [24]. Recently, Muralidhar et al. reported on the efficient one-pot iodine and caesium carbonate assisted synthesis of 3-aminoindole derivatives [25]. Despite these advancements, more diversified synthetic methods are needed to address the ever increasing demand 3-aminoindoles and the related heterocycles. Thus, here, we present a one-pot palladium-

catalysed Sonogashira type nucleophilic annulative amination reaction of 2-iodoanilines in the absence of ligands and a copper co-catalyst to form 3-aminoindole derivatives (Scheme 2).

2. Results and Discussion

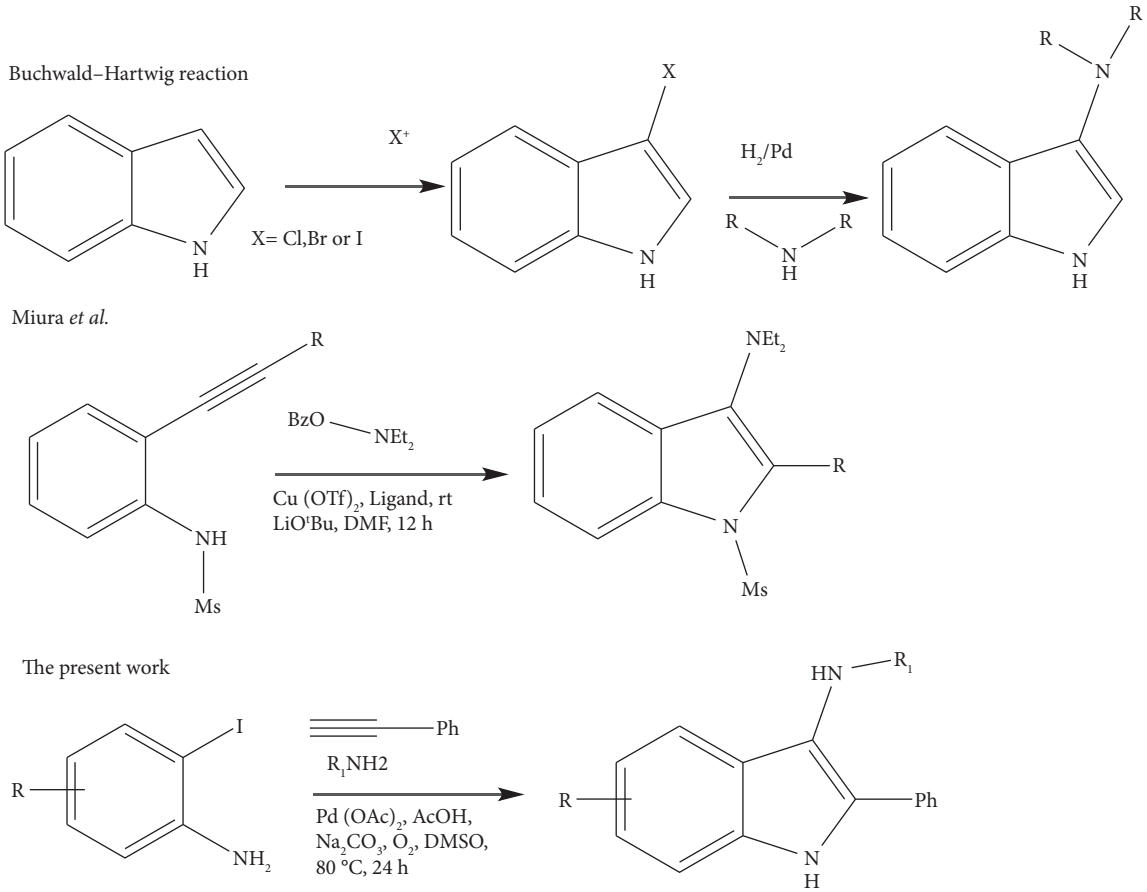
2.1. Chemistry. Sonogashira cross-coupling is a palladium-catalysed sp^2–sp coupling reaction between aryl or alkenyl halides or triflates and terminal alkynes. The reaction is usually carried out using a palladium catalyst, copper co-catalyst, a base, and supporting ligands such as triphenylphosphine [26]. Despite the application of this methodology, the use of copper can lead to homo-coupling of the terminal alkyne while triphenylphosphine oxide from the oxidised triphenylphosphine ligand can be difficult to remove from the resulting cross-coupling [27]. To circumvent the formation of the Songashira byproducts, several methods were developed to address this. Such synthetic methods were reported by Soheili et al. [28], Mpungose and co-workers [29], Dewan and co-investigators [30], Nikoshvili et al. [31], Gholap et al. [32], and Lehr and co-workers [33].

We started our investigations with 2-iodoanaline **5** and phenylacetylene **6** as model substrates for the copper- and ligand-free Sonogashira type reaction (Scheme 3). We used tetrabutylammonium fluoride (TBAF) and dimethylsulfoxide (DMSO) as a starting base and solvent, respectively (Table 1). The use of TBAF and DMSO is well-documented [31, 33]. The use of palladium chloride together with hydrochloric acid favoured the formation of alkyne **7** (entry 1), while the use of palladium triflouroacetate returned starting materials (entry 2). With the preliminary disappointing results, the introduction of palladium acetate ($Pd(OAc)_2$), acetic acid (AcOH), and TBAF yielded promising results where indole product **8** was produced favourably in 21% yield (entry 3). Interestingly, increasing the equivalence of TBAF resulted in the increased yield of the indole product (entries 4–8). Thus, the best results were obtained when 6 equivalence of TBAF was used, giving the indole product **8** an almost 90% yield (entry 8). Motivated by these results, more bases were also investigated for improved results (100% of indole). Disappointingly, the use of caesium and potassium carbonates resulted in the reduced yield of the indole product (entries 9 and 10). When sodium carbonate was used as a base, the indole product was obtained in 96% without the trace of the alkyne product **7** (entry 11). Thus, we have successfully developed an optimum copper- and ligand-free Sonogashira type reaction that will be applied in the preparation of 3-aminoindoles.

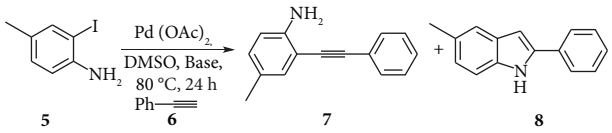
After successfully optimising the formation of the indole product **8** under ligand- and copper-free Sonogashira type reaction, the optimum reaction conditions were then used to prepare 3-amnoindole derivatives. Thus, 2-iodoaniline **9** was treated with phenylacetylene **6**, various amines, palladium acetate, sodium carbonate, acetic acid, and DMSO as a solvent, and the reaction mixture was stirred at 80°C for 24 hours (Scheme 4). Fortunately, the reaction proceeded smoothly to produce a variety of 3-aminoindole derivatives in poor to excellent yields. For example, when 2-bromo-6-iodo-4-methylaniline **9a** was used together with 3,5-dichloroaniline, 3-aminoindole derivative **10a** was obtained with an 80% yield while benzylamine gave 3-aminoindole derivative **10b** in a fair yield of 68% (Table 2). Similarly, 2-iodoaniline **9b** was treated with 3,5-dichloroaniline, 4-(trifluoromethoxy) benzylamine, benzylamine, 4-(trifluoromethoxy) aniline, and pyrrolidine to give 3-aminoindole derivatives with the best yield of 98% (Table 2). To increase the substrate scope, 5-flouro-2-iodoaniline **9c** and 5-chloro-2-iodoaniline **9d** were also included in the study. When **9c** was used as the starting material, 3-aminoindole derivatives **10i** and **10j** were obtained in 50 and 83% yield, respectively, while the use of **9d** produced 3-aminoindole derivatives in fair (50%) to excellent (89%) yields. Lastly, 4-amino-3-iodobenzonitrile **9e** was also used to further increase the scope of the reaction. This produced 3-aminoindole derivatives **10p–t**, where **10r** was obtained in a poor yield of 41%, while **10t** was obtained with an excellent yield of 95% (Table 2). Despite several attempts to optimise the yields of benzylamine-containing 3-aminoindole derivatives, the best yield obtained was for product **10f** (73% yield), while other products were obtained with poor to fair yields. The successful synthesis of all 3-aminoindole products was confirmed using ^1H and ^{13}C nuclear magnetic resonance spectroscopy (NMR) used together with Fourier transform infrared (FTIR) spectroscopy and mass spectroscopy (MS). The 3-aminoindole derivatives were biologically evaluated as potential tuberculosis and malaria therapeutic agents.

2.2. Biological Evaluations

2.2.1. Anti-Mycobacterium tuberculosis Assay. Tuberculosis (TB), a communicable disease that is caused by the bacillus *Mycobacterium tuberculosis* (Mtb), is the leading cause of death as a result of a single infectious agent worldwide even overtaking HIV/AIDS. World Health Organisation (WHO) has reported that the emergence of COVID-19 has negatively affected the TB management system. This increased the number of people who developed TB in 2020. In addition, all previously set goals of completely eradicating TB including incidence rate, death rate, and cost reduction for the treatment of TB aimed at the year 2020 were not met. To help WHO meet its goals of eradicating TB by the year 2035, more intensified research and innovative treatment methods are needed especially in identifying new drugs that can also treat drug-resistant TB strains such as multidrug and extended-drug TB [34]. Previously, we have reported the use of novel benzylated sulfamethoxazole and benzylamine derivatives as potential anti-*Mycobacterium tuberculosis* agents [35, 36]. Indole derivatives as potential antituberculosis agents are well-documented. For example, Stec et al. reported on indole-2-carboxamides derivatives [37, 38], Cihan–Üstündağ and co-workers discovered spirocyclic indole derivatives [39] and indole-based hydrazide-hydrazones [40] as potential antituberculosis remedies. Encouraged by the above information and in our continued efforts to discover new compounds with antitubercular activity, here, we present the *in vitro* antitubercular activity of new 3-aminoindole derivatives.



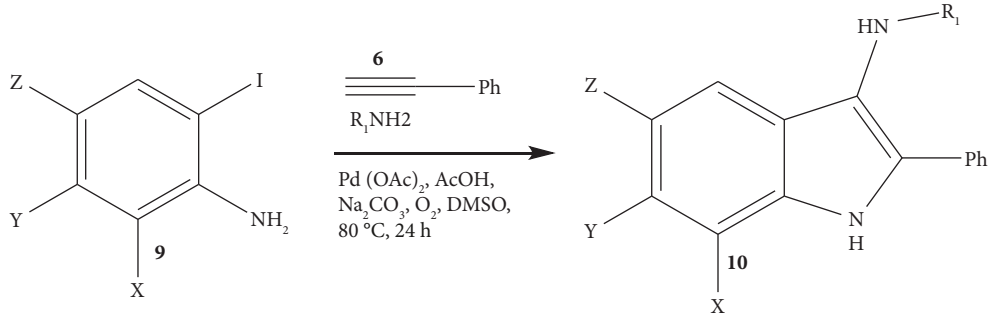
Scheme 2: Approaches to 3-aminoindole derivatives.



Scheme 3: Copper- and ligand-free Sonogashira type reaction.

Table 1: Copper- and ligand-free Sonogashira type reaction to produce indole **8** from 2-iodoaniline **5**.

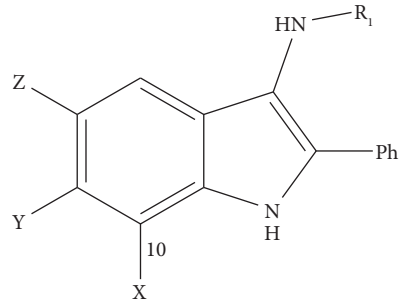
Entry	Solvent	Pd (II) cat.	Acid	Salt	Time (h)	T (°C)	Yield (%)	
							7	**8**
1	DMSO	$PdCl_2$	HCl	TBAF	24	80	15	0
2	DMSO	Pd $(OF_3Ac)_2$	AcOH	TBAF	24	80	0	0
3	DMSO	Pd $(OAc)_2$	AcOH	TBAF	24	80	12	21
4	DMSO	Pd $(OAc)_2$	AcOH	TBAF (2 eq.)	24	80	13	28
5	DMSO	Pd $(OAc)_2$	AcOH	TBAF (3 eq.)	24	80	21	50
6	DMSO	Pd $(OAc)_2$	AcOH	TBAF (4 eq.)	24	80	18	60
7	DMSO	Pd $(OAc)_2$	AcOH	TBAF (5 eq.)	24	80	10	70
8	DMSO	Pd $(OAc)_2$	AcOH	TBAF (6 eq.)	24	80	3.4	89
9	DMSO	Pd $(OAc)_2$	AcOH	Cs_2CO_3 (6 eq.)	24	80	73	22
10	DMSO	Pd $(OAc)_2$	AcOH	K_2CO_3 (6 eq.)	24	80	55	41
11	DMSO	Pd $(OAc)_2$	AcOH	Na_2CO_3 (6 eq.)	24	80	0	96
12	DMSO	Pd $(OAc)_2$	AcOH	Et_3N (6 eq.)	24	80	6	86



X = Br, H
Y = Cl, F, H
Z = CN, H, Me

Scheme 4: Synthetic route to access 3-aminoindole derivatives **10**.

Table 2: 3-Aminoindole derivatives and their percentage yields.



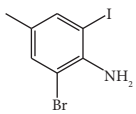
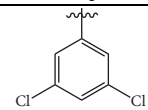
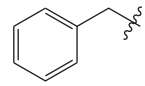
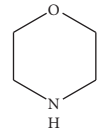
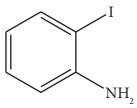
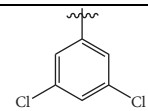
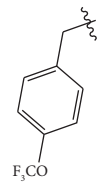
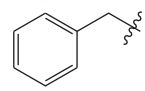
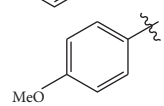
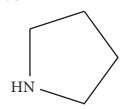
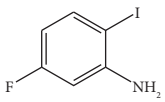
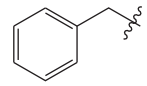
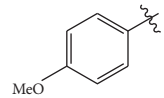
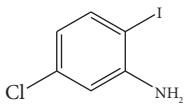
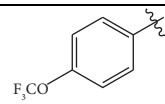
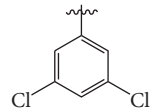
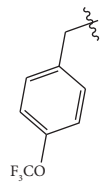
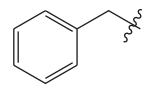
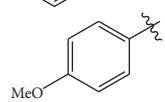
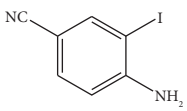
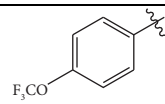
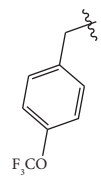
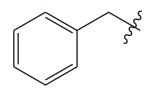
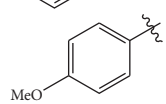
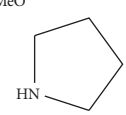
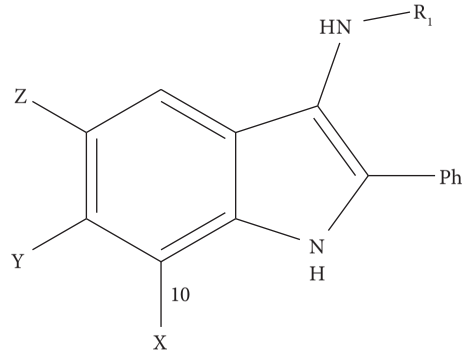
Iodoaniline 9	R_1	10 (% Yield)
 **9a**		**10a** (80)
		**10b** (68)
		**10c** (80)
 **9b**		**10d** (83)
		**10e** (70)
		**10f** (73)
		**10g** (70)
		**10h** (98)

Table 2: Continued.

 **9c**		**10i** (50)
		**10j** (83)
 **9d**		**10k** (66)
		**10l** (75)
		**10m** (89)
		**10n** (50)
		**10o** (83)
 **9e**		**10p** (65)
		**10q** (76)
		**10r** (41)
		**10s** (81)
		**10t** (95)

All synthesised compounds were evaluated for their biological activity against the *Mycobacterium tuberculosis* (*Mtb*) $H_{37}R_V$ strain using the CAS and ADC media. [41] The biological assays were performed following a broth dilution method in 7H9_CAS_GLU_TX and 7H9_ADC_GLU_TW with rifampicin being used as a positive control. [42] The anti-*Mycobacterium tuberculosis* results are displayed in Table 3. The results in Table 3 show that 3-aminoindole derivatives possessed mixed antitubercular activity in the two media used. Thus, some compounds displayed activity only in the CAS media while other compounds showed activity only in the ADC media. For example, 3-amino indole derivatives **10a** (7.813 μM), **10d** (15.625 μM), and **10f** (21.874 μM) showed strong antitubercular activity while **10n** (62.500 μM), **10o** (62.500 μM), and **10r** (32.354 μM) showed weak antitubercular activity in the CAS medium. On the other hand, compounds **10c** (21.590 μM), **10i** (17.076 μM), **10j** (8.332 μM), **10o** (15.373 μM), and **10t** (20.970 μM) showed excellent antitubercular activity in the ADC medium. The most active indole derivative in the CAS

Table 3: Anti-*Mycobacterium tuberculosis*, antiplasmodial, and cytotoxicity assays of the 3-aminoindole derivatives **10a–t**.



Structure	MIC$_{90}$ (μM) Mtb $H_{37}R_V$ strain		% Survival Plasmodium falciparum (Nf54)	Cytotoxicity IC$_{50}$ (μg/ml)		
	7H9_CAS_GLU T_X	7H9_ADC_GLU T_X		Raw 264.7 mouse macrophages	Skin KMST-6 human cells	Kidney Hek-293 human cells
10a	7.813	>125	77.5	>100	>100	>100
10b	125	>125	80.7	>100	>100	>100
10c	—	21.590	70.3	>100	>100	>100
10d	15.625	>125	88.9	>100	>100	>100
10e	7.955	15.503	84.9	>100	>100	>100
10f	21.874	>125	84.1	>100	>100	>100
10g	125	>125	85.6	>100	>100	>100
10h	—	62.5	83.1	>100	>100	>100
10i	125	17.076	85.9	>100	>100	>100
10j	>125	8.332	65.6	>100	>100	>100
10k	>125	>125	76.5	>100	>100	>100
10l	125	>125	76.3	>100	>100	>100
10m	125	>125	81.3	>100	>100	>100
10n	62.5	>125	82.6	>100	>100	>100
10o	62.5	15.373	85.1	>100	>100	>100
10p	>125	>125	77.8	>100	>100	>100
10q	32.354	62.5	87.1	>100	>100	>100
10r	31.864	125	78.8	>100	>100	>100
10s	9.514	16.043	77.5	>100	>100	>100
10t	—	20.970	81.1	>100	>100	>100
Rifampicin	0.001	0.02	—			
Chloroquine	—	—	0.007			
Curcumin (μM)	—	—	—	50	50	52.5

medium was **10a** with a MIC_{90} value of 7.813 μM while **10j** with a MIC_{90} value of 8.332 μM was the most active indole derivative in the ADC medium. In addition, only two compounds showed strong antitubercular activity in both media. Indole derivative **10e** showed an activity of 7.995 μM in the CAS medium, while the activity decreased by almost half in the ADC medium to 15.503 μM. Similarly, 3-aminoindole derivative **10s** possessed the antitubercular activity of 9.514 μM in the CAS medium while the activity dropped in the ADC medium to 16.043 μM. Surprisingly, only 3-aminoindole derivative **10o** showed an increase in antitubercular activity in the CAS medium of 62.500 μM to 15.373 μM in the ADC medium, a four-fold increase.

2.2.2. Anti-Plasmodium falciparum Assay. Malaria, mainly caused by *Plasmodium falciparum* and to some extent *Plasmodium vivax*, is the major parasitic ailment that mostly affects tropical and subtropical regions. Malaria is estimated to infect more than 400 million individuals per year while killing over 1 million annually. As such, more intensified research efforts are underway to find drugs that can cure the disease or minimise its transmission. The most common drug targets to treat malaria are dihydrofolate reductase enzyme (responsible for the *Plasmodium falciparum*'s DNA synthesis) and histone deacetylase enzymes (responsible for the regulation of transcription and assembling the newly synthesis ex-chromatin material). Recently, Manganyi and co-workers investigated chromone-carboxylate derivatives as potential antimalarial agents [43]. Indole and its derivatives are well-documented motifs in the search for compounds with antimalarial properties [44]. Due to malaria being a continued health threat, the search for alternative compounds that present potential remedies is of great importance. Thus, the synthesised 3-aminoindole derivatives were explored as potential antimalarial agents.

The 3-aminoindole derivatives were tested over 72 hours against the wild-type drug sensitive strain (Nf54) of the human malaria parasite *Plasmodium falciparum* [45] and the quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using the reported method and the results are displayed in Table 3 [46]. Analysis of the antiplasmodial activity results in Table 3 shows that 3-aminoindole derivatives were not strong potential antimalarial agents. For example, the most active compound in this series was derivatives **10c** and **10j** displaying a survival rate of 70.3% and 65%, respectively. In addition, derivatives **10k** and **10l** displayed a pathogen survival rate of 76%, compounds **10a**, **10p**, **10r**, and **10s** displayed a pathogen survival rate of less than 78% while the rest of the compounds showed a survival rate of more than 80%. The least effective compound was **10d** which showed a survival rate of 89%. All the compounds were evaluated at a concentration of 20 μM. In addition to the antitubercular and antimalarial activities, cytotoxicity of all compounds was also performed. The cytotoxicity results in Table 3 were represented as the concentration at which 50% of cells are inhibited (IC_{50}). The IC_{50} could not be determined because the inhibitory percentages were higher than 100% and indicating that the compounds were noncytotoxic to all cell lines tested.

2.3. Structure-Activity Relationship and Predicted ADMET Properties. The effect of substituents on the antitubercular and antimalarial properties of the 3-aminoindoles was examined. For example, compounds containing 3,5-dichloroaniline were active with the exception of **10l** and the inactivity can be attributed to the presence of 6-chloro substituent on the indole nucleus. In addition, the use of benzylamine (**10b**, **10f**, **10i**, **10n**, and **10r**) produced mostly active compounds except for **10b,** and the poor activity of **10b** can be due to the presence of 5-methyl and 7-bromo substituents on the indole nucleus. The lack of substituents on the indole nucleus improved antitubercular activity when 4-trifluoromethoxybenzylamine was used. For example, 3-aminoindole **10e** possessed antitubercular activity in both media used. The lack of substituents on the indole nucleus led to diminished activity when 4-methoxybenzylamine was used. For instance, 3-aminoindole **10g** lost activity while **10j** with 6-fluoro substituent on the indole nucleus showed the best antitubercular activity in the ADC medium and the best antimalarial activity of the whole series. Moreover, 3-aminoindole derivatives **10o** and **10s** showed antitubercular activity in the ADC medium.

Physiochemical properties (adsorption, distribution, metabolism, excretion, and toxicity (ADMET)) of the synthesised compounds were analysed using the online prediction software ADMETlab 2.0 [47, 48]. The predicted physiochemical properties will help us estimate the behaviour of the synthesised compounds after consumption and the results are displayed in Table 4. Unfortunately, all 3-aminoindole derivatives displayed poor predicted LogS and LogP values. Similarly, all compounds showed strong protein binding properties and failed to satisfy the GSK and Pfizer drug discovery rules. Topological polar surface area (TPSA) is one of the main properties used in Pfizer's drug discovery rules. Most compounds displayed a low TPSA value of 27.82 while other compounds displayed values lower than 75 as recommended by Pfizer. For example, compounds **10e**, **10g**, **10j**, **10k**, **10m**, and **10o** all displayed slightly improved TPSA values of 37.05 while other compounds displayed much improved TPSA values (**10t**, 42.82; **10r**, 51.61; **10p**, **10q** and **10s**, 60.84). In addition, the majority of the compounds (**10e** and **10i–t**) were predicted to be the human Ether-à-go-go-related gene (hERG) blockers. Moreover, compounds **10e**, **10k**, **10m**, and **10p–t** were all predicted to possess strong human hepatotoxicity (H-HT) properties. All compounds satisfied Lipinski's rule of drug discovery with the number of hydrogen acceptors (nHA) and the number of hydrogen donors (nHD) of all compounds falling within the maximum predicted values.

3. Experimental Procedures

3.1. General Procedures. Unless specifically indicated, all experiments were performed under oxygen atmosphere. All reagents were of reagent grade and were used as acquired with no extra purification. Solvents were used as purchased. The structural properties of the compounds were recorded and confirmed by: high-resolution mass spectroscopy using Waters Synapt G2, ESI probe, ESI Pos, Cone Voltage 15 V

Table 4: ADMET predictions of 3-aminoindole derivatives **10a–t**.

Structure	MW (g/mol)	Predicted ADMET properties								Rules satisfied		
		LogS	LogP	Plasma protein binding (PPB) (%)	nHA	nHD	H-HT	hERG blocker	TPSA	Lipinski	Pfizer	GSK
10a	443.98	−7.79	7.08	101.7	2	2	0.19	0.18	27.82	Yes	No	No
10b	390.07	−6.72	5.86	99.83	2	2	0.25	0.25	27.82	Yes	No	No
10c	370.07	−6.39	4.98	97.63	3	1	0.28	0.069	28.26	Yes	No	No
10d	352.05	−7.20	6.43	100.6	2	2	0.21	0.56	27.82	Yes	No	No
10e	382.13	−6.30	5.88	100.7	3	2	0.97	0.89	37.05	Yes	No	No
10f	298.15	−5.53	4.88	99.57	2	2	0.38	0.43	27.82	Yes	No	No
10g	314.14	−6.61	5.34	99.38	3	2	0.41	0.53	37.05	Yes	No	No
10h	262.15	−5.85	4.93	97.36	2	1	0.24	0.43	19.03	Yes	No	No
10i	316.14	−5.66	4.98	100.1	2	2	0.58	0.70	27.82	Yes	No	No
10j	332.13	−6.72	5.45	99.73	3	2	0.59	0.74	37.05	Yes	No	No
10k	402.07	−7.38	6.76	101.3	3	2	0.97	0.86	37.05	Yes	No	No
10l	386.01	−7.52	6.86	101.6	2	2	0.16	0.70	27.82	Yes	No	No
10m	416.09	−6.71	6.40	101.5	3	2	0.96	0.91	37.05	Yes	No	No
10n	332.11	−6.16	5.54	100.1	2	2	0.22	0.70	27.82	Yes	No	No
10o	348.10	−7.10	5.95	99.97	3	2	0.30	0.76	37.05	Yes	No	No
10p	393.11	−7.19	6.08	100.8	4	2	0.99	0.92	60.84	Yes	No	No
10q	407.12	−6.50	5.66	101.1	4	2	0.99	0.94	60.84	Yes	No	No
10r	323.14	−5.83	4.52	100.2	3	2	0.88	0.82	51.61	Yes	No	No
10s	339.14	−6.89	5.05	99.86	4	2	0.88	0.87	60.84	Yes	No	No
10t	287.14	−6.38	4.61	97.75	1	2	0.86	0.87	42.82	Yes	No	No

MW-molecular weight: 100–600 g/mol, LogS (predicted aqueous solubility): −4–0.5 log mol/L, LogP (predicted octanol/water partition coefficient): 0–3, human hepatotoxicity (H H-T): 0 (nontoxic)–+1 (toxic), hERG blockers: 0 (inactive)–+1 (active), protein plasma binding (PPB): <90%, number of hydrogen acceptors (nHA): 0–12, number of hydrogen donors (nHD): 0–7, GSK's rule: MW ≤ 400, LogP ≤4, Pfizer's rule: LogP ≤3, topological polar surface area (TPSA) >75, Lipinski's rule: MW ≤500, LogP ≤5, number of hydrogen acceptors (nHA) ≤10, number of hydrogen donors (nHD) ≤5.

(Waters Corp., Milford, MA, USA) at the University of Stellenbosch Central Analytical Facility; melting points were obtained using Lasec/SA-melting point apparatus from Lasec company, SA (Johannesburg, South Africa); FTIR spectra were recorded using Bruker Technologies Alpha Platinum ATR FTIR spectrometer and nuclear magnetic resonance (NMR) (Bruker Ascend 400 MHz Topspin 3.2); ^{1}H NMR and ^{13}C NMR spectra were referenced internally using solvent signals, ^{1}H NMR: 7.250 ppm for $CDCl_3$, 2.500 ppm for DMSO-d_6; ^{13}C NMR: 77.00 ppm for $CDCl_3$, 39.40 ppm for DMSO-d_6, respectively which were used as the solvents at room temperature. Chemical shifts are expressed in δ-values parts per million (ppm) and the coupling constants (J) in Hertz (Hz). Multiplicity of the signals is given as follows: brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, and m = multiplet.

*3.1.1. Synthesis of 3-Aminoindole Derivatives **10a–t**.* General synthetic procedure for copper-free and ligand-free Sonogashira cross-coupling reaction is given as follows.

2-Iodoaniline derivative **9** (0.10 g) was reacted with phenylacetylene **6** (1.0 eq.), palladium acetate (0.1 eq.), acetic acid (1.0 eq.), sodium carbonate (6.0 eq.), and amine derivative (1.0 eq.) in DMSO (20 mL) at 80°C and stirred for 24 hour under oxygen balloon. The mixture was mixed with water (50 mL), extracted thrice with 30 mL of ethyl acetate, dried using anhydrous magnesium sulphate, excess solvent removed under vacuum, analysed using thin layer chromatography (TLC), and then purified by flash chromatography (20–30% EtOAc/hexane) to give 3-aminoindole derivatives **10a–t**.

*3.1.2. Synthesis of 7-Bromo-N-(3,5-Dichlorophenyl)-5-Methyl-2-Phenyl-1H-Indol-3-Amine **10a**.* Reagents: 2-Bromo-4-methyl-6-iodoaniline (0.100 g, 0.32 mmol), phenyl acetylene (1.0 eq. 0.04 mL, 0.32 mmol), Pd $(OAc)_2$ (0.1 eq., 6.68 mg, 32.1 μmol), acetic acid (1.0 eq., 19.2 mg, 0.32 mmol), sodium carbonate (6.0 eq., 0.203 g, 1.92 mmol), 3,5-dichloroaniline (1 eq., 51.94 mg, 0.32 mmol), and DMSO (20 mL). Black powder (0.099 g, 0.22 mmol, 70%), M.p. = 102–104°C, ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.25 (s, 1H), 7.56 (m, 2H), 7.43 (m, 3H), 7.33 (d, J = 7.9 Hz, 1H), 7.24 (m, 1H), 7.078 (s, 1H), 6.68 (dd, J = 2.2 Hz, 2H), 4.45 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 143.1, 138.6, 138.1, 136.9, 133.8, 133.5, 132.6, 131.3, 129.1, 128.5, 128.1, 125.9, 125.5, 122.9, 121.8, 120.7, 119.6, 113.7, 103.9, 100.5, 21.2, V_{max} (FTIR) 3200, 1850, 1450, 750, and 620 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{15}BrCl_2N_2$): 446.1690: $[M + H]^+$. Found: 446.1660 $[M + H]^+$.

*3.1.3. Synthesis of N-Benzyl-7-Bromo-5-Methyl-2-Phenyl-1H-Indol-3-Amine **10b**.* Reagents: 2-Bromo-4-methyl-6-iodoaniline (0.1 g, 0.32 mmol), phenyl acetylene (1.0 eq.

0.04 mL, 0.32 mmol), Pd $(OAc)_2$ (0.1 eq., 6.68 mg, 32.1 μmol), acetic acid (1.0 eq., 19.2 mg, 0.32 mmol) sodium carbonate (6.0 eq., 0.203 g, 1.92 mmol), benzylamine (1.0 eq., 0.04 mL, 0.32 mmol) and DMSO (20 mL). Dark green powder (0.085 g, 0.21 mmol, 68%), M.p. = 119–121°C. Proton (^{1}H) NMR (400 MHz, $CDCl_3$, ppm): δ_H 8.39 (s, 1H), 7.52 (m, 4H), 7.4 (m, 2H), 7.34 (m, 5H), 7.24 (s, 1H), 4.82 (s, 2H), 4.55 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 142.8, 138.6, 137.6, 136.3, 133.6, 132.0, 130.6, 128.8, 128.5, 128.1, 128.0, 125.0, 122.4, 121.2, 119.1, 116.3, 115.2, 110.7, 103.5, 100.9, 53.2, 20.5; V_{max} (FT-IR) 3245, 1850, 1465, 1450, 620 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{19}BrN_2$): 391.3120: $[M + H]^+$. Found: 391.2061 $[M + H]^+$.

3.1.4. Synthesis of 4-(7-Bromo-5-Methyl-2-Phenyl-1H-Indol-3-yl) Morpholine ***10c***. Reagents: 2-Bromo-4-methyl-6-iodoaniline (0.1 g, 0.32 mmol), phenyl acetylene (1.0 eq. 0.04 mL, 0.32 mmol), Pd $(OAc)_2$ (0.1 eq., 6.68 mg, 32.1 μmol), acetic acid (1.0 eq., 19.2 mg, 0.32 mmol) sodium carbonate (6.0 eq., 0.203 g, 1.92 mmol), morpholine (1.0 eq., 0.03 mL, 0.32 mmol), and DMSO (20 mL). Black powder (0.095 g, 0.26 mmol, 80%), M.p. = 67–69°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.70 (s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.62 (m, 2H), 7.52 (d, J = 8.0 Hz, 3H), 3.89 (s, 4H), 2.61 (s, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm); δ_C 138.8, 132.6, 131.5, 129.1, 128.5, 128.1, 125.9, 125.4, 119.0, 103.9, 100.5, 60.5, 40.8, 31.0; V_{max} (FT-IR) 3250, 2920, 1850, 1465, 1450, 1250, 650 cm^{-1}. HRMS (ESI) calculated for ($C_{19}H_{19}BrN_2O$): 371.2780: $[M + H]^+$. Found: 371.1900 $[M + H]^+$.

3.1.5. Synthesis of N-(3,5-Dichlorophenyl)-2-Phenyl-1H-Indol-3-Amine ***10d***. Reagents: 2-Iodoaniline (0.1 g, 0.46 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.46 mmol), Pd $(OAc)_2$ (0.1 eq., 9.51 mg, 0.46 μmol), acetic acid (1.0 eq., 27.6 mg, 0.46 mmol), sodium carbonate (6.0 eq., 0.291 g, 2.76 mmol), 3,5-dichloroaniline (1.0 eq., 74.53 mg, 0.46 mmol), and DMSO (20 mL). Black powder (0.135 g, 0.38 mmol, 83%), M.p. = 99–102°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.47 (s, 1H), 7.66 (m, 2H), 7.43 (m, 3H), 7.31 (s, 1H), 7.18 (dd, J = 1.0 Hz, 1H), 7.12 (m, 2H), 6.71 (s, 1H), 6.52 (d, J = 1.7 Hz, 2H), 4.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 148.3, 137.9, 135.5, 131.8, 129.1, 128.9, 128.5, 127.7, 127.3, 125.5, 125.2, 122.4, 120.7, 120.4, 120.3, 118.3, 118.1, 113.3, 111.0, 99.9; V_{max} (FT-IR) 3250, 1850, 700 cm^{-1}. HRMS (ESI) calculated for ($C_{20}H_{14}Cl_2N_2$): 353.2460: $[M + H]^+$. Found: 353.1534$[M + H]^+$.

3.1.6. Synthesis of N-(4-(Trifluoromethoxy) Benzyl)-2-Phenyl-1H-Indol-3-Amine ***10e***. Reagents: 2-Iodoaniline (0.1 g, 0.46 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.46 mmol), Pd $(OAc)_2$ (0.1 eq., 9.51 mg, 0.46 μmol),, acetic acid (1.0 eq., 27.6 mg, 0.46 mmol), sodium carbonate (6.0 eq., 0.291 g, 2.76 mmol), 4-trifluoromethoxy benzylamine (1.0 eq., 87.93 mg, 0.46 mmol), and DMSO (20 mL). Chocolate brown powder (0.123 g, 0.32 mmol, 70%), M.p. = 75–77°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.63 (s, 1H), 7.65 (m, 2H), 7.53 (m, 2H), 7.32 (m, 3H), 7.15 (d, J = 2.0 Hz, 2H), 6.72 (dd, J = 1.0 Hz, 2H), 6.63 (dd, J = 1.4 Hz, 2H), 4.69 (s, 2H), 4.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 160.6, 137.8, 137.8, 136.8, 134.3, 132.4, 129.7, 124.4, 129.1, 128.9, 128.5, 128.1, 122.2, 121.0, 120.8, 120.5, 120.1, 119.9, 114.7, 110.9, 99.7, 47.8; V_{max} (FT-IR) 3300, 1850, 1465, 1390, 1250 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{17}F_3N_2O$): 382.3862: $[M + H]^+$. Found: 382.2580 $[M + H]^+$.

3.1.7. Synthesis of N-Benzyl-2-Phenyl-1H-Indol-3-Amine ***10f***. Reagents: 2-Iodoaniline (0.1 g, 0.46 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.46 mmol), Pd $(OAc)_2$ (0.1 eq., 9.51 mg, 0.46 μmol),, acetic acid (1.0 eq., 27.6 mg, 0.46 mmol) sodium carbonate (6.0 eq., 0.291 g, 2.76 mmol), benzylamine (1.0 eq., 0.05 mL, 0.46 mmol), and DMSO (20 mL). Chocolate brown powder (0.10 g, 0.34 mmol, 73%) M.p. = 83–85°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.28 (s, 1H), 7.49 (dd, J = 1.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.34 (m, 8H), 7.23 (dd, J = 1.6 Hz, 2H), 4.74 (dd, J = 1.0 Hz, 2H), 4.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 139.5, 139.1, 136.3, 136.1, 132.7, 129.5, 129.9, 128.7, 128.7, 123.5, 121.8, 120.0, 118.1, 111.5, 99.8, 43.7; V_{max} (FT-IR) 3210, 1850, 1460 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{18}N_2$): 298.3890: $[M + H]^+$. Found: 298.3680 $[M + H]^+$.

3.1.8. Synthesis of N-(4-Methoxyphenyl)-2-Phenyl-1H-Indol-3-Amine ***10g***. Reagents: 2-Iodoaniline (0.1 g, 0.46 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.46 mmol), Pd $(OAc)_2$ (0.1 eq., 9.51 mg, 0.46 μmol),, acetic acid (1.0 eq., 27.6 mg, 0.46 mmol) sodium carbonate (6.0 eq., 0.291 g, 2.76 mmol), *para*-anisidine (1.0 eq., 56.65 mg, 0.46 mmol) and DMSO (20 mL). Black powder (0.101 g, 0.32 mmol, 70%), M.p. = 83–85°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.59 (s, 1H), 7.51 (m, 2H), 7.41 (m, 3H), 7.33 (m, 4H), 6.71 (m, 2H), 6.63 (d, J = 8.8, 2H), 4.28 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 152.7, 139.8, 132.5, 132.1, 131.4, 129.6, 128.9, 128.3, 122.2, 120.6, 120.1, 117.9, 116.4, 114.7, 110.9, 99.8, 55.7; V_{max} (FT-IR) 3250, 1850, 1460, 1450, 1250 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{18}N_2O$): 314.3880: $[M + H]^+$. Found: 313.2641 $[M + H]^+$.

3.1.9. Synthesis of 2-Phenyl-3-(Pyrrolidin-1-yl)-1H-Indole ***10h***. Reagents: 2-Iodoaniline (0.1 g, 0.46 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.46 mmol), Pd$(OAc)_2$ (0.1 eq., 9.51 mg, 0.46 μmol),, acetic acid (1.0 eq., 27.6 mg, 0.46 mmol) sodium carbonate (6.0 eq., 0.291 g, 2.76 mmol), pyrolidine (1.0 eq., 0.04 mL, 0.46 mmol), and DMSO (20 mL). Dark green powder (0.118 g, 0.45 mmol, 98%), M.p. = 94–96°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.63 (s, 1H), 7.67 (d, J = 8.0, 2H), 7.42 (m, 5H), 7.18 (m, 2H), 2.61 (s, 4H), 2.04 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 137.9, 136.9, 132.5, 128.5, 127.7, 125.2, 122.3, 120.6, 120.2, 111.0, 99.9, 40.9, 31.2; V_{max} (FT-IR) 3050, 2950, 1850 cm^{-1}. HRMS (ESI)

calculated for ($C_{18}H_{18}N_2$): 262.3560: $[M+H]^+$.Found: 262.1824 $[M+H]^+$.

3.1.10. Synthesis of N-Benzyl-6-Fluoro-2-Phenyl-1H-Indol-3-Amine ***10i***. Reagents: 5-Fluoro-2-iodoaniline (0.1 g, 0.42 mmol), phenyl acetylene (1.0 eq., 43.09 mg, 0.42 mmol), $Pd(OAc)_2$ (0.1 eq., 8.79 mg, 0.422 μmol),, acetic acid (1.0 eq., 25.2 mg, 0.42 mmol), sodium carbonate (6.0 eq., 0.266 g, 2.52 mmol), benzylamine (1.0 eq., 0.05 mL, 0.42 mmol), and DMSO (20 mL). Black solid (0.053 g, 0.17 mmol, 40%), M.p. = 142–144°C. ^{1}H NMR (400 MHz, DMSO, ppm); δ_H 8.07 (s, 1H), 7.91 (t, J = 7.3 Hz, 1H), 7.66 (dd, J = 2.0 Hz, 2H), 7.45 (m, 8H), 6.98 (d, J = 8.6 Hz, 2H), 5.74 (s, 2H), 5.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO, ppm): δ_C 153.5, 140.7, 138.7, 136.7, 133.7, 131.9, 129.5, 129.0, 125.8, 122.5, 119.6, 114.6, 106.2, 99.8, 55.4; V_{max} (FT-IR) 3250, 1800, 1460, 1400 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{17}FN_2$): 316.3794: $[M+H]^+$. Found: 316.3140 $[M+H]^+$.

3.1.11. Synthesis of 6-Fluoro-N-(4-Methoxyphenyl)-2-Phenyl-1H-Indol-3-Amine ***10j***. Reagents: 5-Fluoro-2-iodoaniline (0.1 g, 0.42 mmol), phenyl acetylene (1.0 eq., 43.09 mg, 0.42 mmol), Pd $(OAc)_2$ (0.1 eq., 8.79 mg, 0.422 μmol), acetic acid (1.0 eq., 25.2 mg, 0.42 mmol), sodium carbonate (6.0 eq., 0.266 g, 2.52 mmol), *p*-anisidine (1.0 eq., 51.72 mg, 0.42 mmol), and DMSO (20 mL). Dark green (0.073 g, 0.23 mmol, 55%), M.p. = 82–84°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 7.95 (s, 1H), 7.59 (d, J = 1.7 Hz, 2H), 7.40 (m, 5H), 6.81 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.8 Hz, 1H), 6.45 (m, 2H), 4.00 (s, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO, ppm): δ_C 152.6, 149.5, 139.7, 138.7, 133.5, 132.3, 128.3, 128.3, 128.1, 121.5, 116.3, 114.6, 105.1, 100.8, 55.5; V_{max} (FT-IR) 3200, 1870, 1450, 1400, 1250 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{17}FN_2O$): 332.3784: $[M+H]^+$. Found: 332.2140 $[M+H]^+$.

3.1.12. Synthesis of 6-Chloro-2-Phenyl-N-(4-(Trifluoromethoxy) Phenyl)-1H-Indol-3-Amine ***10k***. Reagents: 5-Chloro-2-iodoaniline (0.1 g, 0.39 mmol), phenyl acetylene (1.0 eq., 0.04 mL, 0.39 mmol), $Pd(OAc)_2$ (0.1 eq., 8.22 mg, 0.395 μmol), acetic acid (1.0 eq., 23.1 mg, 0.39 mmol) sodium carbonate (6.0 eq., 0.247 g, 2.34 mmol), 4-trifluoromethoxy aniline (1.0 eq., 0.05 mL, 0.39 mmol), and DMSO (20 mL). Brown solid (0.088 g, 0.22 mmol, 56%), M.p. = 94–96°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.49 (s, 1H), 7.51 (m, 3H), 7.43 (m, 2H), 7.35 (m, 2H), 7.07 (dd, J = 2.0 Hz, 1H), 6.78 (dd, J = 1.0 Hz, 2H), 6.71 (d, J = 2.4 Hz, 2H), 4.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 147.7, 139.6, 138.6, 137.1, 135.1, 131.9, 129.0, 128.9, 128.5, 128.3, 127.9, 127.9, 127.7, 125.1, 121.4, 121.3, 120.9, 119.9, 114.2, 110.8, 99.8; V_{max} (FT-IR) 3230, 1845, 1250, 1400, 820 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{14}ClF_3N_2O$): 402.800: $[M+H]^+$. Found: 404.500 $[M+H]^+$.

3.1.13. Synthesis of 6-Chloro-N-(3,5-Dichlorophenyl)-2-Phenyl-1H-Indol-3-Amine ***10l***. Reagents: 5-Chloro-2-iodoaniline (0.1 g, 0.39 mmol), phenyl acetylene (1.0 eq., 0.04 mL, 0.39 mmol), Pd $(OAc)_2$ (0.1 eq., 8.22 mg, 0.395 μmol), acetic acid (1.0 eq., 23.1 mg, 0.39 mmol) sodium carbonate (6.0 eq., 0.247 g, 2.34 mmol), 3,5-dichloroaniline (1.0 eq., 63.19 mg, 0.39 mmol) and DMSO (20 mL). Brown powder (0.098 g, 0.25 mmol, 65%), M.p. = 90–92°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.84 (s, 1H), 7.51 (m, 2H), 7.41 (m, 2H), 7.32 (m, 3H), 7.05 (dd, J = 2.0 Hz, 1H), 6.69 (m, 1H), 6.50 (d, J = 8.0 Hz, 2H), 4.18 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 148.4, 139.6, 138.7, 137.2, 135.4, 132.5, 131.9, 129.1, 128.5, 127.9, 125.2, 121.4, 120.9, 118.2, 113.2, 110.9, 99.7; V_{max} (FT-IR) 3050, 1850, 840 cm^{-1}. HRMS (ESI) calculated for ($C_{20}H_{13}Cl_3N_2$): 387.690: $[M+H]^+$. Found: 387.182 $[M+H]^+$.

3.1.14. Synthesis of N-(4-(Trifluoromethoxy) Benzyl)-6-Chloro-2-Phenyl-1H-Indol-3-Amine ***10m***. Reagents: 5-Chloro-2-iodoaniline (0.1 g, 0.39 mmol), phenyl acetylene (1.0 eq., 0.04 mL, 0.39 mmol), Pd $(OAc)_2$ (0.1 eq., 8.22 mg, 0.395 μmol), acetic acid (1.0 eq., 23.1 mg, 0.39 mmol) sodium carbonate (6.0 eq., 0.247 g, 2.34 mmol), 4-trifluoromethoxy benzylamine (1.0 eq., 0.06 mL, 0.39 mmol), and DMSO (20 mL). Brown powder (0.145 g, 0.35 mmol, 89%), M.p. = 67–69°C. ^{1}H NMR (400 MHz, CDCl3, ppm); δ_H 8.41 (s, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.38 (m, 4H), 7.29 (d, J = 7.6, 3H), 7.23 (d, J = 8.2 Hz, 3H), 4.83 (s, 2H), 4.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 160.9, 139.4, 136.3, 132.3, 131.4, 128.9, 128.3, 128.3, 124.9, 121.1, 120.7, 119.7, 114.0, 110.8, 99.5, 41.2; V_{max} (FT-IR) 3200, 1800, 1230, 1400, 1450, 850 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{16}ClF_3N_2O$): 416.8282: $[M+H]^+$. Found: 416.7150 $[M+H]^+$.

3.1.15. Synthesis of N-Benzyl-6-Chloro-2-Phenyl-1H-Indol-3-Amine 10n. Reagents: 5-Chloro-2-iodoaniline (0.1 g, 0.39 mmol), phenyl acetylene (1.0 eq., 0.04 mL, 0.39 mmol), Pd $(OAc)_2$ (0.1 eq., 8.22 mg, 0.395 μmol), acetic acid (1.0 eq., 23.1 mg, 0.39 mmol) sodium carbonate (6.0 eq., 0.247 g, 2.34 mmol), benzylamine (1.0 eq., 0.04 mL, 0.39 mmol), and DMSO (20 mL). Chocolate brown solid (0.065 g, 0.19 mmol, 50%), M.p. = 73–75°C. ^{1}H NMR (400 MHz, DMSO, ppm); δ_H 7.62 (s, 1H), 7.71 (dd, J = 1.2 Hz, 2H), 7.58 (m, 6H), 7.42 (m, 2H), 7.35 (m, 3H), 5.44 (s, 1H), 4.61 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 139.6, 138.7, 137.3, 135.1, 131.4, 129.0, 128.4, 127.9, 125.2, 121.4, 120.8, 119.8, 118.1, 114.2, 110.9, 99.6, 53.5; V_{max} (FT-IR) 3220, 1830, 1420, 820 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{17}ClN_2$): 332.8310: $[M+H]^+$. Found: 332.6572 $[M+H]^+$.

3.1.16. Synthesis of 6-Chloro-N-(4-Methoxyphenyl)-2-Phenyl-1H-Indol-3-Amine ***10o***. Reagents: 5-Chloro-2-iodoaniline (0.1 g, 0.39 mmol), phenyl acetylene (1.0 eq., 0.04 mL, 0.39 mmol), Pd $(OAc)_2$ (0.1 eq., 8.22 mg, 0.395 μmol), acetic acid (1.0 eq., 23.1 mg, 0.39 mmol) sodium carbonate (6.0 eq., 0.247 g, 2.34 mmol), *p*-anisidine (1.0 eq., 48.03 mg, 0.39 mmol) and DMSO (20 mL). Brown solid (0.11 g, 0.31 mmol, 83%), M.p = 90–92°C. δ_H (400 MHz, $CDCl_3$, ppm); δ 7.57 (s, 1H), 7.56 (t, J = 6.8 Hz, 3H), 7.34 (m, 5H),

6.76 (d, $J = 8.8$ Hz, 2H), 6.67 (d, $J = 8.8$ Hz, 2H), 4.38 (s, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 160.7, 138.9, 137.4, 135.3, 133.1, 129.0, 128.5, 127.8, 125.3, 121.2, 120.6, 118.0, 114.1, 111.3, 99.2, 58.5; V_{max} (FT-IR) 3300, 1810, 1450, 1245, 820 cm^{-1}. HRMS (ESI) calculated for ($C_{21}H_{17}ClN_2O$): 348.8300: $[M + H]^+$. Found: 348.6021 $[M + H]^+$.

3.1.17. Synthesis of 3-(4-(Trifluoromethoxy) Phenylamino)-2-Phenyl-1H-Indole-5-Carbonitrile ***10p***. Reagents: 4-Amino-3-iodobenzonitrile (0.1 g, 0.41 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.41 mmol), $Pd(OAc)_2$ (0.1 eq., 8.53 mg, 0.41 μmol), acetic acid (1.0 eq., 24.6 mg, 0.41 mmol) sodium carbonate (6.0 eq., 0.261 g, 2.46 mmol), 4-trifluoromethoxy aniline (1.0 eq., 0.06 mL, 0.41 mmol) and DMSO (20 mL). Black solid (0.089 g, 0.23 mmol, 65%), M.p. = 93–95°C. ^{1}H NMR (400 MHz, DMSO, ppm); δ_H 8.06 (s, 1H), 7.92 (m, 1H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.43 (m, 5H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 5.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO, ppm): δ_C 153.5, 139.3, 138.8, 136.7, 133.7, 131.9, 129.5, 129.1, 128.9, 125.8, 124.7, 122.8, 122.4, 122.1, 119.6, 114.6, 112.9, 101.9, 99.7; V_{max} (FT-IR) 3020, 2250, 1850, 1400, 1220 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{14}F_3N_3O$): 393.3692: $[M + H]^+$. Found: 393.2116 $[M + H]^+$.

3.1.18. Synthesis of 3-(4-(Trifluoromethoxy) Benzylamino)-2-Phenyl-1H-Indole-5-Carbonitrile ***10q***. Reagents: 4-Amino-3-iodobenzonitrile (0.1 g, 0.41 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.41 mmol), $Pd(OAc)_2$ (0.1 eq., 8.53 mg, 0.41 μmol), acetic acid (1.0 eq., 24.6 mg, 0.41 mmol) sodium carbonate (6.0 eq., 0.261 g, 2.46 mmol), 4-trifluoromethoxy benzylamine (1.0 eq., 0.07 mL, 0.41 mmol) and DMSO (20 mL). Brown solid (0.110 g, 0.27 mmol, 76%), M.p. = 68–70°C. ^{1}H NMR (400 MHz, DMSO, ppm); δ_H 9.2 (s, 1H), 7.83 (d, $J = 8.8$ Hz, 3H), 7.71 (d, $J = 8.8$, 3H), 7.35 (m, 6H), 4.62 (s, 1H), 4.40 (d, $J = 6.0$, 2H). ^{13}C NMR (100 MHz, DMSO, ppm): δ_C 161.4, 137.2, 136.3, 136.1, 135.9, 133.2, 129.4, 129.1, 128.5, 128.5, 122.3, 121.2, 119.5, 113.9, 110.7, 99.7, 46.2; V_{max} (FT-IR) 3250, 2055, 1850, 1465, 1400, 1250 cm^{-1}. HRMS (ESI) calculated for ($C_{23}H_{16}F_3N_3O$): 407.3962: $[M + H]^+$. Found: 407.2553 $[M + H]^+$.

3.1.19. Synthesis of 3-(Benzylamino)-2-Phenyl-1H-Indole-5-Carbonitrile ***10r***. Reagents: 4-Amino-3-iodobenzonitrile (0.1 g, 0.41 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.41 mmol), Pd $(OAc)_2$ (0.1 eq., 8.53 mg, 0.41 μmol), acetic acid (1.0 eq., 24.6 mg, 0.41 mmol) sodium carbonate (6.0 eq., 0.261 g, 2.46 mmol), benzylamine (1.0 eq., 0.05 mL, 0.41 mmol) and DMSO (20 mL). Brown powder (0.041 g, 0.13 mmol, 41%), M.p. = 162–164°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 7.70 (s, 1H), 7.47 (d, $J = 1.5$ Hz, 1H), 7.41 (m, 3H), 7.22 (m, 9H), 4.79 (s, 2H), 4.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 142.5, 140.2, 138.5, 132.9, 131.4, 128.7, 128.3, 125.3, 122.1, 119.4, 113.8, 111.8, 99.6, 99.4, 46.9; V_{max} (FT-IR) 3200, 2050, 1845, 1465 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{17}N_3$): 323.3990: $[M + H]^+$. Found: 322.2150 $[M + H]^+$.

3.1.20. Synthesis of 3-(4-Methoxyphenylamino)-2-Phenyl-1H-Indole-5-Carbonitrile 10s. Reagents: 4-Amino-3-iodobenzonitrile (0.1 g, 0.41 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.41 mmol), $Pd(OAc)_2$ (0.1 eq., 8.53 mg, 0.41 μmol), acetic acid (1.0 eq., 24.6 mg, 0.41 mmol) sodium carbonate (6.0 eq., 0.261 g, 2.46 mmol), *p*-anisidine (1.0 eq., 50.49 mg, 0.41 mmol) and DMSO (20 mL). Black powder (0.099 g, 0.29 mmol, 71%), M.p. = 79–81°C. ^{1}H MNR (400 MHz, $CDCl_3$, ppm); δ_H 8.34 (s, 1H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.54 (m, 2H), 7.36 (m, 5H), 6.74 (d, $J = 8.8$, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 4.45 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 151.2, 139.9, 138.2, 136.3, 133.2, 128.9, 128.7, 128.6, 128.5, 126.5, 122.6, 122.4, 122.3, 116.5, 115.5, 114.8, 113.9, 99.9, 99.8, 55.7; V_{max} (FT-IR) 3250, 2050, 1850, 1450, 1200 cm^{-1}. HRMS (ESI) calculated for ($C_{22}H_{17}N_3O$): 339.3890: $[M + H]^+$. Found: 339.1987$[M + H]^+$.

3.1.21. Synthesis of 2-Phenyl-3-(Pyrrolidin-1-yl)-1H-Indole-5-Carbonitrile ***10t***. Reagents: 4-amino-3-iodobenzonitrile (0.1 g, 0.41 mmol), phenyl acetylene (1.0 eq., 0.05 mL, 0.41 mmol), Pd $(OAc)_2$ (0.1 eq., 8.53 mg, 0.41 μmol), acetic acid (1.0 eq., 24.6 mg, 0.41 mmol) sodium carbonate (6.0 eq., 0.261 g, 2.46 mmol), pyrolidine (1.0 eq., 0.03 mL, 0.41 mmol), and DMSO (20 mL). Dark green solid (0.112 g, 0.39 mmol, 95%), M.p. = 135–138°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm); δ_H 8.34 (s, 1H), 7.65 (s, 1H), 7.55 (m, 2H), 7.39 (m, 5H), 2.62 (s, 4H), 1.88 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ_C 136.1, 133.0, 132.3, 129.1, 128.7, 128.3, 128.3, 125.5, 122.2, 121.6, 119.3, 113.8, 99.6, 52.5, 25.6; V_{max} (FT-IR) 3300, 2950, 2045, 1850 cm^{-1}. HRMS (ESI) calculated for ($C_{19}H_{17}N_3$): 287.3660: $[M + H]^+$. Found: 287.2480 $[M + H]^+$.

3.1.22. Evaluation of the Antitubercular Activity. The test samples were prepared in 100% DMSO at a stock concentration of 10 mM stock. These were tested for growth inhibition of the H37Rv strain of *Mycobacterium* (Mtb) using the Alamar blue assay in a single point (20 μM) screen. On each test plate the controls used were a minimum growth control (Rifampicin at 2X MIC: 0.150 μM), and a maximum growth control (DMSO). The final concentration of DMSO was always less than 5%. The culture of *M. tuberculosis* was grown to an optical density (OD600) of 0.5–0.7. A volume of 50 μl of the diluted culture was added to each well of each test plate, for a final volume of 100 μl per well. The assay plate was incubated at 37°C with 5% CO_2 and humidification. Alamar Blue reagent was added to each well of the assay plate 24 h prior to the assay end date, after which the assay was re-incubated for 24 h. The relative fluorescence units (RFU) (excitation 540 nm; emission 590 nm) of each well was measured using a SpecraMax i3x Plate reader on day 8 (Serial no. 36370 3271, Molecular Devices Corporation 1311 Orleans Drive Sunnyvale, California). Data analysis was performed using the Dotmatics software. The on-board "Fluorescent Intensity–Endpoint" protocol is used in conjunction with the following wavelength filters: excitation: 540 emission: 590. Raw RFU data were

normalised to the minimum and maximum inhibition controls (% inhibition) using the Levenberg–Marquardt damped least-squares method.

3.1.23. Evaluation of the Antiplasmodial Activity. The test samples were prepared to a 10 mmol/L stock solution in 100% DMSO. Samples were tested as a suspension if not completely dissolved. Further dilutions were prepared in growth media on the day of the experiment. The standard antimalarial drugs chloroquine (CQ) and artesunate (Arts) were used as the reference drug in all experiments. A full dose-response was performed for standard compounds in a 96-well plate to determine the concentration inhibiting 50% of parasite growth (IC_{50}–value). Test samples were tested at a concentration of 20 μmol/L and 2 μmol/L, while CQ and Arts were tested from a starting concentration of 1 μg/mL. The highest concentration of solvent to which the parasites were exposed was <0.1% and has no measurable effect on the parasite viability (data were not shown). The assay plate was incubated at 37°C for 72 h in a sealed gas chamber under 3% O_2 and 4% CO_2 with the balance being N_2. After 72 h, the wells in the assay plate were gently resuspended, and 15 μL from each well was transferred to a duplicate plate containing 100 μL of Malstat reagent and 25 μL of nitroblue tetrazolium solution in each well. Plates were left to develop for 20 minutes in the dark and then the absorbance of each well was quantified using a spectrophotometer at 620 nM wavelength. The remaining population of parasites at each concentration of the test compound was determined by comparing the absorbance of each well to the absorbance of a well containing the drug-free control. Survival was plotted against concentration and the IC_{50} values were obtained using a nonlinear dose-response curve fitting analysis via the Dotmatics software platform.

3.1.24. Evaluation of the Cytotoxicity Activity. The cytotoxicity of the 3-aminoindole derivatives on the Raw 264.7 mouse macrophages, skin KMST-6, and kidney Hek-293 human cell lines was determined using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay [49]. All cell lines were cultured in Dulbecco's modified eagles medium (DMEM; Hyclone Laboratories, South Logan, USA), containing fetal bovine serum (FBS; Gibco Life Technologies Massachusetts, USA) and 1% antibiotic mixture of penicillin and streptomycin (Biowest, USA), at 37°C in a humidified incubator with 5% CO_2 atmosphere. Cells (1.0×10^5/well) were seeded in 96-well plates, incubated overnight to attach, and treated for 24 h with various concentrations (31.2, 15.6, and 7.8 µg/ml) of the compounds, 0.2% DMSO and 50 µM curcumin. After treatment, 1 mg/ml of MTT diluted in complete media was added to each well and incubated for a further 4 h. The media was discarded, 100 μl DMSO (>99.9%) was added to each well, and absorbance was measured at 560 nm using a GloMax®-Multi + Detection system microtiter plate reader (Promega, USA) [50].

4. Conclusion

The Sonogashira cross-coupling reaction that did not employ copper cocatalyst and ligands were successfully developed and subsequently used to access valuable 3-aminoindole derivatives. The resulting 3-aminoindole derivatives were biologically assessed against *Mycobacterium tuberculosis* and *Plasmodium falciparum*. In addition, the 3-aminoindole derivatives were assayed for their cytotoxicity against different cell lines. Moreover, the structure activity relationship of the compounds was determined to assess the impact of substituents on the biological activity of the 3-aminoindole derivatives. Lastly, drug-like properties of the 3-aminonindoles were estimated using online prediction software ADMETlab 2.0, and all compounds failed both Pfizer's and GSK's drug discovery rules.

Data Availability

The data used to support the findings of the study are available from the corresponding author upon request at Tlabo.leboho@ul.ac.za.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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