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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, and SAR studies of new (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide derivatives as possible antimicrobial and antitubercular agents

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Abstract In this article, we report herein the SAR studies of a series of (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide **10**(**a**–**j**), **11**(**a**–**j**). The synthesized compounds were evaluated for their preliminary in vitro antibacterial, antifungal activity and were screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The synthesized compounds displayed interesting antimicrobial activity.

Keywords Indole · Antibacterial activity · Anti fungal activity · Antimycobacterial

Introduction

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), is a tenacious and remarkably successful pathogen that has latently infected a third of the world population. The increasing emergence of drug resistant TB and HIV infection, which compromises host defense and allows latent infection to reactivate or render individuals more susceptible to TB, pose further challenges for effective control of the disease (Corbett, 2003). Due to the heterogeneous bacterial populations in the TB lesions and perhaps also to insufficient host immunity, treatment with a combination of drugs must be given for extended periods of time to prevent reactivation of disease by persisting bacilli. The increasing problem of MDR-TB has focused attention on developing new drugs that are not only active against drug resistant TB, but also shorten the lengthy therapy. In developing new TB drugs, it is crucial to think about which target in the tubercle bacillus are good targets.

Heterocyclic compounds play an important role in an untiring effort aimed at developing new antimicrobial agents with new mechanism of action. These heterocyclic compounds well known to possess diverse pharmacological properties, like anti-inflammatory, anticancer anticonvulsant, antimalarial, etc. An extensive literature survey reveals that apart from these biological activities, some of the heterocyclic compounds like derivatives of pyrrole (Mariangela *et al*., 2009), benzimidazole (Charansingh *et al*., 2008), indole (Subramanian *et al*., 2009), imidazole (Jyoti *et al*., 2009), furan (Tangallapally *et al*., 2004), benzotriazole (Dixit *et al*., 2006) showed excellent antimycobacterial properties. In addition, among the heterocyclic compounds, indole derivatives are significant because of their wide spectrum of biological activities. For well over 100 years, the synthesis and functionalization of indole have been a major area of focus for synthetic organic chemist, and numerous methods for the preparation of indoles have been developed (Humphrey and Kuethe, 2006a; Tois *et al*., 2003a; Gribble, 2000; Pindur and Adam, 1998). Among the synthetic methodologies reported so far for the preparation of the indole analogs, the Fischer indole synthesis still maintain its prominent role for the large scale production of biologically active compounds (Siu *et al*., 2004). The indole nucleus is an important structure in numerous natural or synthetic alkaloids and in medicinal

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chemistry. The diversity of the structures encountered as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient, and selective synthetic strategies particularly for the synthesis of substituted indole rings (Tois *et al*., 2003b). The substituted indoles have been referred to as privileged structures since they are capable of binding to many receptors with high affinity (Horton *et al*., 2003). Therefore, the synthesis and selective functionalization of indoles have been the focus of active research (Humphrey and Kuethe, 2006b). In this article, we report herein the SAR studies of a series of (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide derivatives. Among the numerous indole derivatives, with biologically active tryptamine and its derivative such as the neurotransmitter serotonin, and the tissue hormone melatonin constitute especially important examples (Hibino and Choshi, 2002).

As a part of our research work on the development of useful synthetic molecules (Ranjith *et al*., 2010) and for new antitubercular agents (Ranjith *et al*., 2012), it has been planned to introduce two indoles in a single molecular frame work with active groups like chloro, trifluoro, etc. at different positions. It has been hoped that the combination of these active molecules in the new molecular design would lead to better antimicrobial agents. In this communication, we report the synthesis of newly designed (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide (**10a–10j**), (**11a–11j**) (Scheme 3) and evaluated these compounds for the antimicrobial and antitubercular activities.

Results and discussion

Chemistry

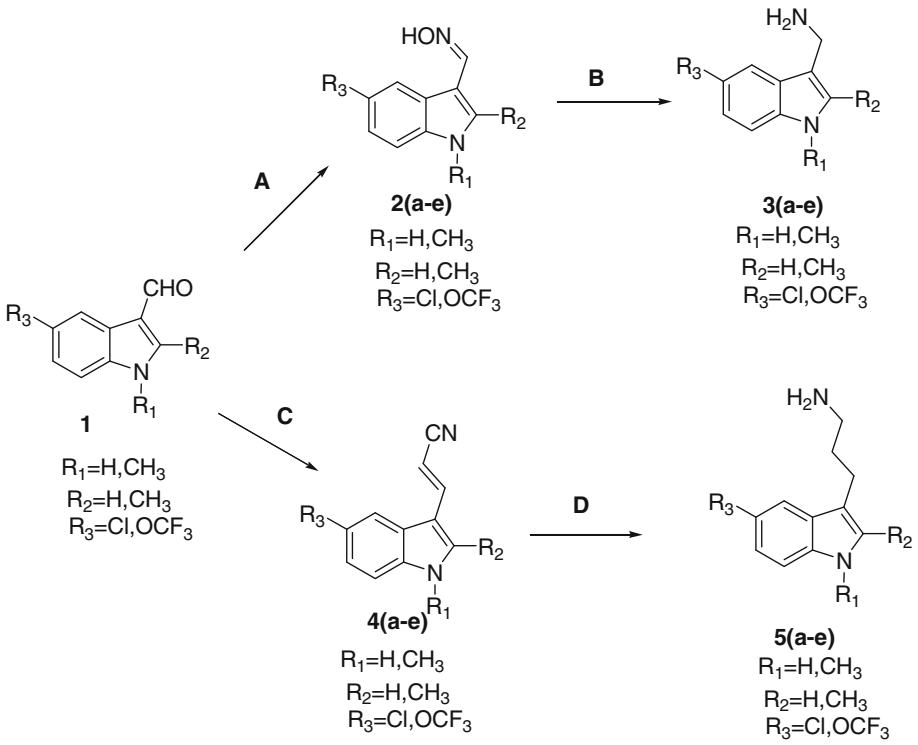
The reaction sequences employed for the synthesis of title compounds are shown in Schemes 1, 2, and 3, respectively. The tryptamine derivatives **3**(**a–e**) were prepared by reacting substituted indole-3-carboxaldehyde **1** and hydroxylamine hydrochloride in methanol heated to 60 °C to get indole-3-methyloxime **2**(**a–e**) which on reduction with raney nickel in alcoholic medium to get **3**(**a–e**). In Scheme 1 substituted indole carboxaldehyde was conveniently converted to **4**(**a–e**) by condensing it with cyanomethyltriphenyl phosphorous bromide, which on reduction using raney nickel heating at 50 °C, 60 psi to form substituted indole-3-propylamine **5**(**a–e**). In Scheme 2 substituted indole-3-carboxaldehyde **1** was conveniently converted to **6** by condensing it with ethoxy carbonyl methyltriphenyl phosphorous bromide, which on reduction using PtO_2 to get **7** which on hydrolysis in alkaline medium to get indole-3-substituted carboxylic acid **9**. The methyl-substituted acid **9** was also prepared in two steps. 5-chloro-1-methyl indole-3-carboxaldehyde treated with malonic acid to form **8** which on reduction using PtO_2 to form 1-methyl-substituted indole-3-carboxylic acid **9**. The title compounds **10**(**a–j**) and **11**(**a–j**) were then synthesized (Scheme 3) by coupling of key intermediates in the presence of EDCI and HOBT (Chan and Cox, 2007). The spectral data are discussed in "Experimental" section.

Structure activity relationship

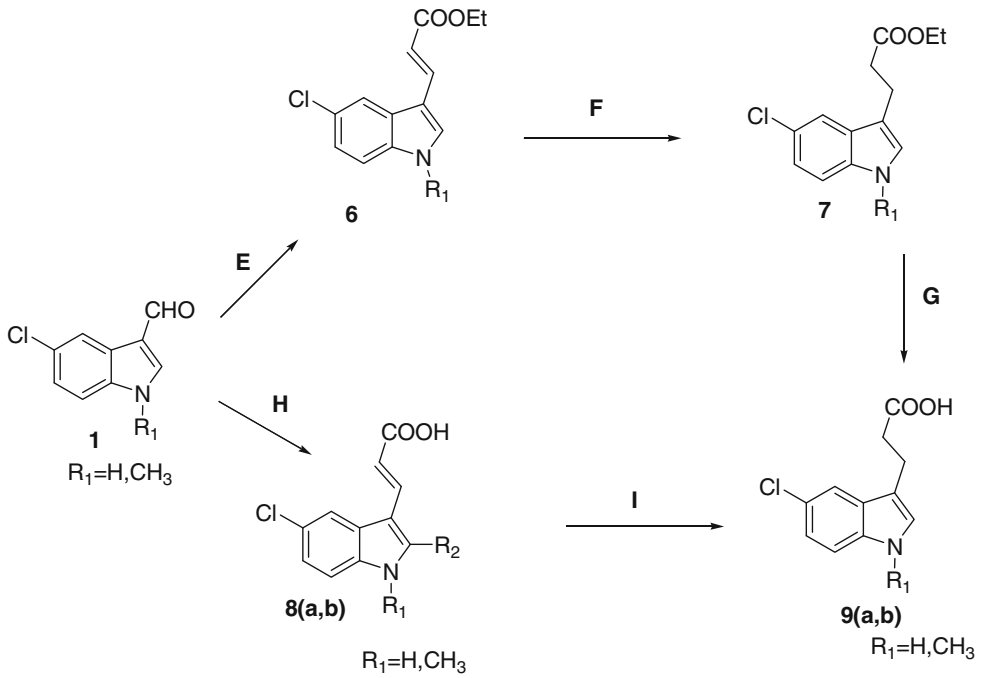
In this study, we have mainly concentrated at the region 1 and region 2 (Fig. 1) of the synthesized molecules. Lipophilicity of compounds plays a vital role in studying the biological activity of a compound (Leo *et al*., 1971). These properties are seen as an important parameter related to membrane permeation in biological system. It has been well established that halogenated particularly $-CF_3$ substituted molecules have got a significant place in modern medicinal chemistry (Nakayama *et al*., 2011). Different substitutions have done at the region 1 of the synthesized molecules (Table 1), e.g., biological results showed that compound **10e** displayed good activity. One of the reasons could be the presence of chloro and $-OCF_3$ group attached to the aryl ring increases the lipophilic nature of the compound, there by making the molecule more cells permeable. The biological results indicated that the compound with electron withdrawing group at the ring at the regions 1 and 2 of the molecule were more active. The unsubstituted –NH at the region 1 of the molecule showed the activity (**10a**, **10b**, **10e**, **10h**, **10i**, **10j**, **11b**, **11i**, and **11j**), but after methyl substitution at the region 1 the activity has been lowered (**10d**, **10g**, **11a**, and **11h**) and the dimethyl substituted compounds show minimal activity (**10c**, **10f**, and **11d**). It has been observed that introduction of $-OCF_3$, chloro substitutions at the ring increases the lipophilicity of the molecule, there by making the molecule more cell permeable and hence enhance the potency of the compounds. Next we shifted our focus on region 2 of the synthesized molecules, at this region methyl substitution at the –NH group found to be active. The SAR studies of the synthesized molecules show that the methyl substitution at the region 1 of the molecule decreases the activity and surprisingly the methyl substitution at the region 2 of the some molecules found to be active (**10e**, **10j**, **11a**, **11e**, **11g**, and **11i**) (Table 2)

Biological activity

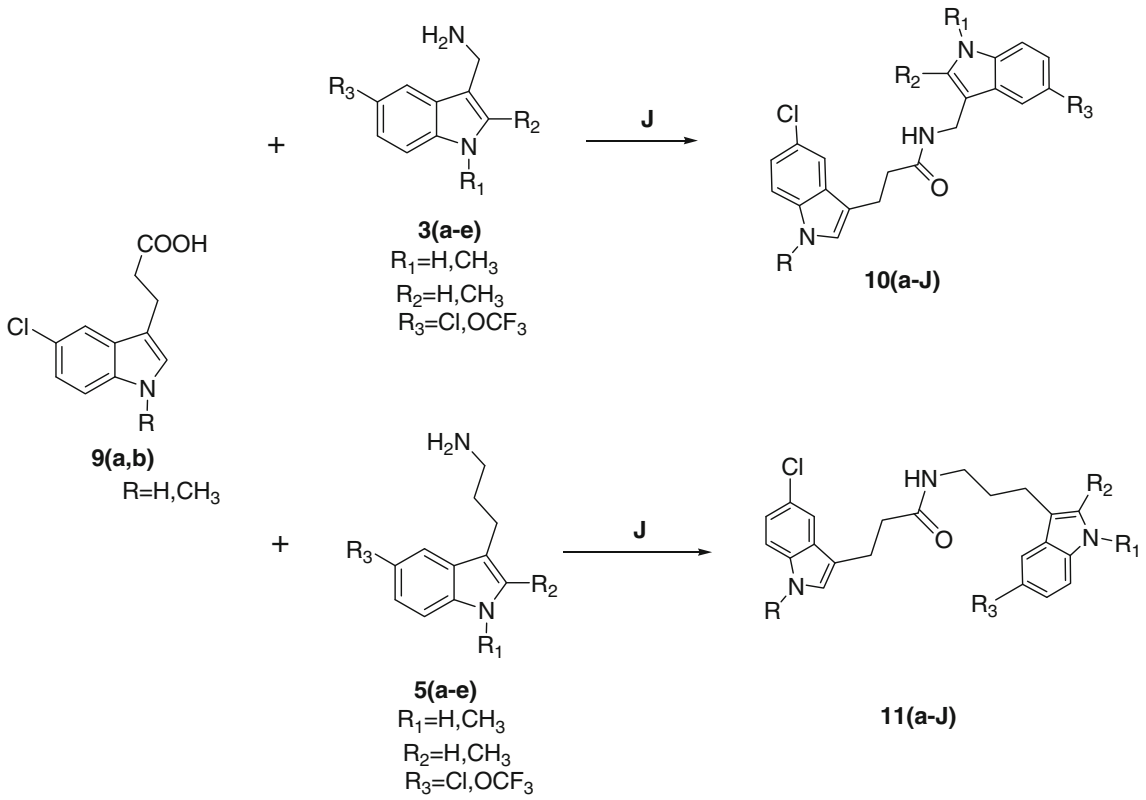
All the title compounds were subjected to in vitro antibacterial, antifungal, and antitubercular properties following standard methods.



Scheme 1 (*A*) $NH_2OH{\cdot}HCl$, C_2H_5OH/Na_2CO_3 60 °C, 3 h. (*B*) Raney Ni/NH_4OH, methanol, 5 h. (*C*) Cyanomethyltriphenylphosphoniumbromide, DBU, toluene, 110 °C, 15 h. (*D*) Raney Ni, CH_3OH, 50 °C, 10 h



Scheme 2 (*E*) Ethoxycarbonylmethyltriphenylphosphoniumbromide, DBU, toluene, 120 °C, 20 h. (*F*) PtO_2, Methanol, H_2, 12 h. (*G*) Ethanol, NaOH, 0 °C. (*H*) Malonic acid, pyridine, piperidine, 115 °C, 14 h. (*I*) PtO_2, H_2, Methanol, 8 h



Scheme 3 (*J*) EDCl/HOBT, TEA, dichloromethane, 25 °C, 3 h

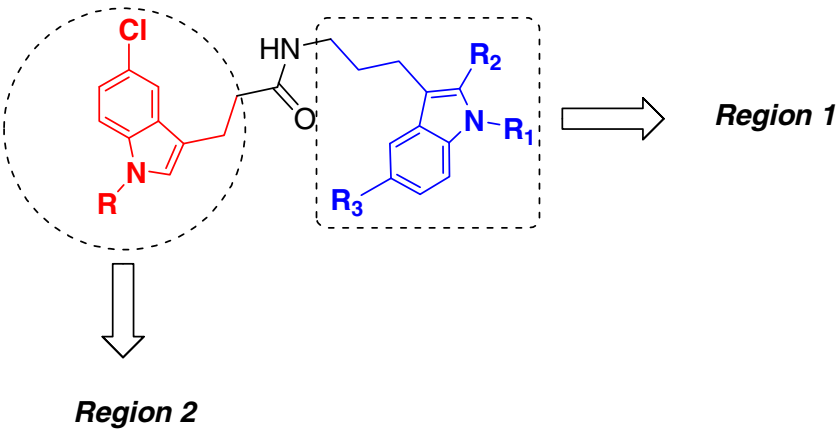


Fig. 1 Selected regions for the SAR studies

Antibacterial activity

Antibacterial activity of the title compounds was investigated against five different bacterial strains, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* using ciprofloxacin as reference, by serial dilution method. Table 2 depicts the antibacterial screening results (MIC, μg/mL) of final compounds, **10**(**a**–**j**) and **11**(**a**–**j**).

Antifngal activity

Antifungal activity of the title compounds was investigated against five different strains, *Aspergillus flavus*, *Aspergillus fumigatus*, *Penicillium marneffei* (recultured), *Trichophyton mentagrophytes* (recultured), and *Candida albicans* using Ciclopirox olamine as reference, by serial dilution method. Table 3 depicts the antifungal screening results (MIC, μg/mL) of final compounds, **10**(**a**–**j**) and **11**(**a**–**j**).

Table 1 Characterization data of synthesized compounds **10**(**a**–**j**) and **11**(**a**–**j**)

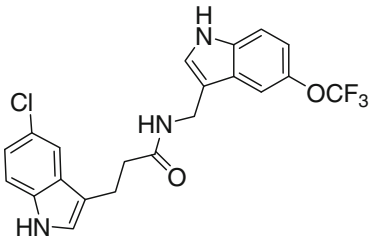
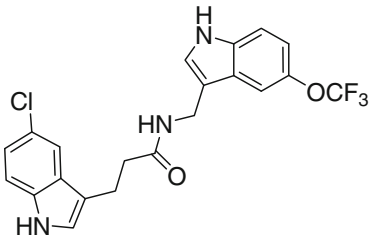
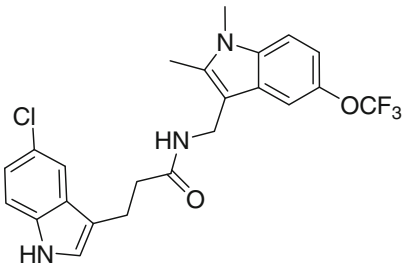
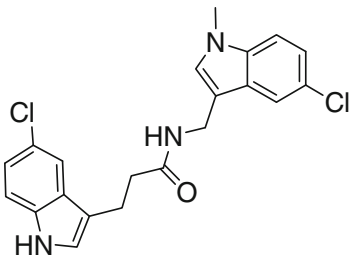
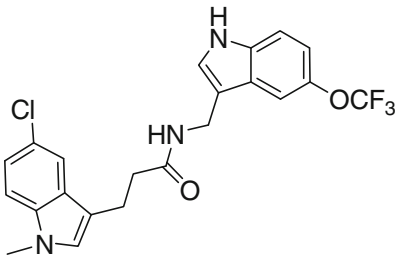
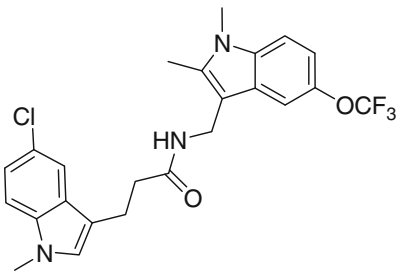
Compounds	Structure	Mol. formula Mol. wt	MP (°C)	Yield (%)[a]
10a		$C_{21}H_{17}ClF_3N_3O_2$ 435.8	213–215	79
10b		$C_{22}H_{19}ClF_3N_3O_2$ 449.8	ND	80
10c		$C_{23}H_{21}ClF_3N_3O_2$ 463.8	261–263	86
10d		$C_{21}H_{19}Cl_2N_3O$ 400.3	209–211	68
10e		$C_{22}H_{19}ClF_3N_3O_2$ 449.8	235–237	70
10f		$C_{24}H_{23}ClF_3N_3O_2$ 477.9	ND	79

Table 1 continued

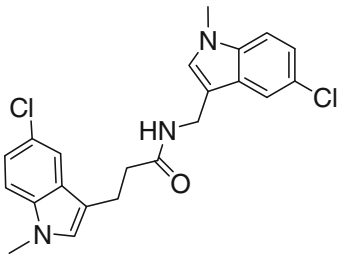
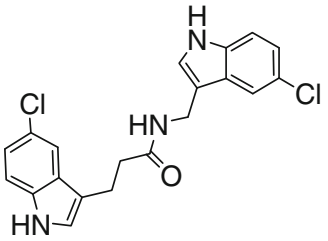
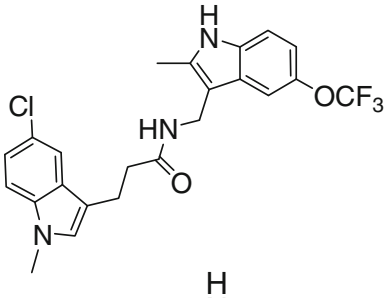
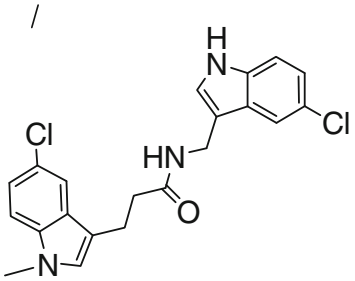
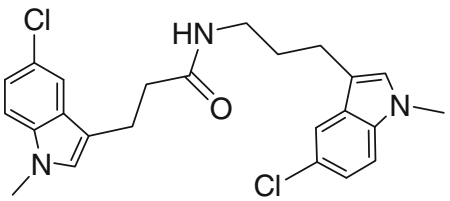
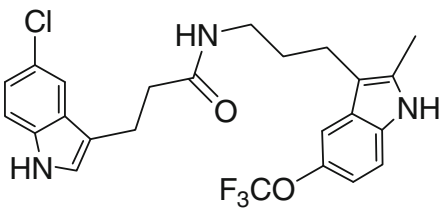
Compounds	Structure	Mol. formula Mol. wt	MP (°C)	Yield (%)[a]
10g		$C_{22}H_{21}Cl_2N_3O$ 414.3	254–256	63
10h		$C_{20}H_{17}Cl_2N_3O$ 386.2	219–221	66
10i		$C_{23}H_{21}ClF_3N_3O_2$ 463.9	ND	73
10j		$C_{21}H_{19}Cl_2N_3O$ 400.3	208–210	80
11a		$C_{24}H_{25}Cl_2N_3O$ 442.4	249–251	71
11b		$C_{24}H_{23}ClF_3N_3O_2$ 478.0	283–285	74

Table 1 continued

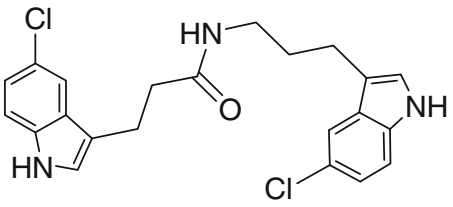
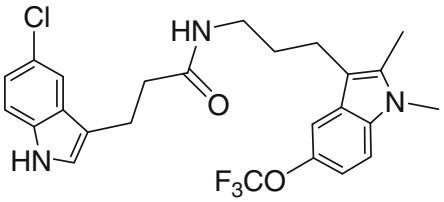
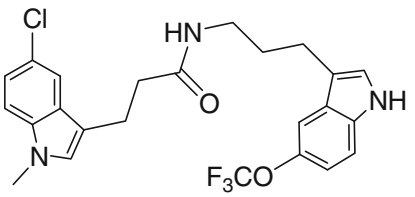
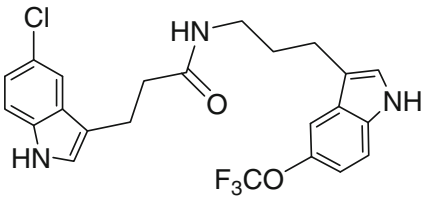
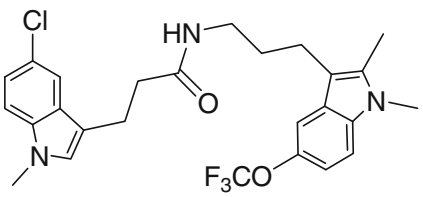
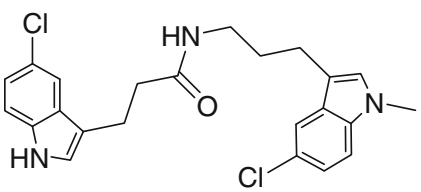
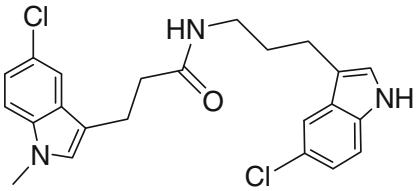
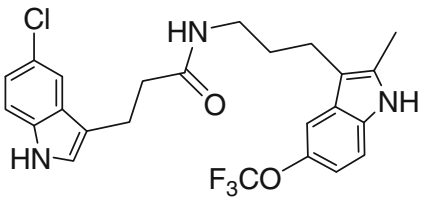
Compounds	Structure	Mol. formula Mol. wt	MP (°C)	Yield (%)[a]
11c		$C_{22}H_{21}Cl_2N_3O$ 414.3	264–266	83
11d		$C_{25}H_{25}ClF_3N_3O_2$ 491.9	ND	89
11e		$C_{24}H_{23}ClF_3N_3O_2$ 477.69	ND	68
11f		$C_{23}H_{21}ClF_3N_3O_2$ 463.8	254–256	82
11g		$C_{26}H_{27}ClF_3N_3O_2$ 505.9	ND	86
11h		$C_{23}H_{23}Cl_2N_3O$ 428.3	238–240	73

Table 1 continued

Compounds	Structure	Mol. formula Mol. wt	MP (°C)	Yield (%)[a]
11i		$C_{23}H_{23}Cl_2N_3O$ 428.3	241–243	79
11j		$C_{24}H_{23}ClF_3N_3O_2$ 477.9	ND	81

ND Not detected

[a] Isolated yield after column purification

Table 2 Antibacterial activity data of the synthesized compounds **10(a–j)** and **11(a–j)**

Compounds	MIC in μg/mL and zone of inhibition in mm				
	S. aureus (ATCC 25923)	*E. coli* (ATCC 24922)	*P. aeruginosa* (ATCC 27853)	*K. pneumoniae* (recultured)	*S. pyogenes*
10a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12.5 (11–15)
10b	6.25 (16–20)	12.5 (11–15)	6.25 (16–20)	25 (<10)	6.25 (16–20)
10c	6.25 (16–20)	12.5 (11–15)	6.25 (16–20)	25 (<10)	25 (<10)
10d	12.5 (11–15)	12.5 (11–15)	25 (<10)	12.5 (11–15)	6.25 (16–20)
10e	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
10f	12.5 (11–15)	12.5 (11–15)	25 (<10)	12.5 (11–15)	25 (<10)
10g	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	25 (<10)
10h	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12.5 (11–15)
10i	25 (<10)	6.25 (16–20)	25 (<10)	6.25 (16–20)	12.5 (11–15)
10j	6.25 (16–20)	6.25 (16–20)	25 (<10))	6.25 (16–20)	6.25 (16–20)
11a	12.5 (11–15)	25 (<10)	25 (<10)	25 (<10)	25 (<10)
11b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
11c	25 (<10)	25 (<10)	25 (<10)	25 (<10))	6.25 (16–20)
11d	12.5 (11–15)	12.5 (11–15)	25 (<10)	12.5 (11–15)	6.25 (16–20)
11e	6.25 (16–20)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	6.25 (16–20)
11f	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12.5 (11–15)
11g	12.5 (11–15)	12.5 (11–15)	25 (<10)	12.5 (11–15)	25 (<10)
11h	25 (<10)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	25 (<10)
11i	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	12.5 (11–15)
11j	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
Ciprofloxacin (standard)	6.25 (30–40)	6.25 (22–30)	6.25 (16–20)	1.56 (21)	6.25 (23–27)

MIC values were evaluated at concentration ranging between 1.56 and 25 μg/mL. The figures in the table show the MIC values in μg/mL and corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit bacterial growth

Table 3 Antifungal activity data of the synthesized compounds **10(a–j)** and **11(a–j)**

Compounds	MIC in μg/mL and zone of inhibition in mm				
	A. flavus (NCIM no. 524)	*A. fumigatus* (NCIM no. 902)	*P. marneffei* (recultured)	*T. mentagrophytes* (recultured)	*Candida albicans*
10a	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
10b	6.25 (16–20)	25 (<10)	6.25 (16–20)	25 (<10)	25 (<10)
10c	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	12.5 (11–15)	6.25 (16–20)
10d	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
10e	6.25 (16–20)	6.25 (16–20)	12.5 (11–15)	25 (<10)	12.5 (11–15)
10f	25 (<10)	6.25 (16–20)	25 (<10)	6.25 (16–20)	12.5 (11–15)
10g	25 (<10)	25 (<10)	12.5 (11–15)	25 (<10)	25 (<10)
10h	25 (<10)	6.25 (16–20)	25 (<10)	6.25 (16–20)	25 (<10)
10i	25 (<10)	25 (<10)	25 (<10)	25 (<10)	12.5 (11–15)
10j	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
11a	12.5 (11–15)	12.5 (11–15)	25 (<10)	12.5 (11–15)	25 (<10)
11b	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
11c	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)	6.25 (16–20)
11d	6.25 (16–20)	25 (<10)	6.25 (16–20)	25 (<10)	12.5 (11–15)
11e	12.5 (11–15)	12.5 (11–15)	25 (<10)	25 (<10)	6.25 (16–20)
11f	25 (<10)	25 (<10)	25 (<10)	25 (<10)	25 (<10)
11g	6.25 (16–20)	12.5 (11–15)	6.25 (16–20)	12.5 (11–15)	25 (<10)
11h	25 (<10)	6.25 (16–20)	25 (<10)	6.25 (16–20)	25 (<10)
11i	25 (<10)	25 (<10)	25 (<10)	12.5 (11–15)	6.25 (16–20)
11j	25 (<10)	25 (<10)	12.5 (11–15)	25 (<10)	25 (<10)
Ciclopirox olamine	6.25 (25–30)	6.25 (25–30)	6.25 (20–27)	6.25 (27–33)	6.25 (20)

MIC values were evaluated at concentration ranging between 6.25 and 25 μg/mL. The figures in the table show the MIC values in μg/mL and corresponding zone of inhibition in mm inside the bracket. MIC (μg/mL) = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit bacterial growth

Antitubercular study

Based on the encouraging results from the antibacterial screening, title compounds were further tested for their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv, *Mycobacterium smegmatis* (ATCC 19420), *Mycobacterium fortuitum* (ATCC 19542), and MDR-TB strains using isoniazid and rifampicin as standards. The screening results of in vitro antimycobacterial activity of the final compounds are tabulated in Table 4.

Biological results

The investigation of antibacterial screening (Table 2) revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **10a**, **10e**, **10h**, **11b**, **11f**, **11i**, and **11j** showed good activity against *E. coli* and *P. aeruginosa*. Compounds **10b**, **10e**, **10j**, **11b**, **11e**, and **11j** showed good activity against *S. aureus* and *S. pyogenes.* Compounds **10a**, **10e**, **10h**, **10i**, **10j**, **11b**, **11f**, **11i**, and **11j** showed good activity against *K. pneumoniae*.

The investigation of antifungal screening (Table 3) revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **10a**, **10b**, **10d**, **10j**, **11b**, **11c**, and **11g** showed good activity against *A. flavus* and *P. marneffei*. Compounds **10a**, **10d**, **10f**, **10h**, **10j**, **11b**, **11c**, and **11h** showed good activity against *T. mentagrophytes* and *A. fumigatus*. Compounds **10a**, **10c**, **10d**, **10j**, **11b**, **11c**, **11e**, and **11i** showed good activity against *C. albicans*. Further, the preliminary antimycobacterial screening of the title compounds was carried out at 1, 10, and 100 μg/mL concentrations against three different TB strains and also against MDR-TB strain. From the result, it was noticed that the compounds **10a**, **10b**, **10e**, **10h**, **10i**, **10j**, **11a**, **11b**, **11d**, **11e**, **11g**, **11i**, and **11j** were active between 1 and 10 μg/mL concentrations against *M. tuberculosis* H37Rv strain. The active compounds from the preliminary investigation were further subjected to second level of testing. The compounds

Table 4 Antitubercular activity data of the synthesized compounds **10(a–j)** and **11(a–j)**

Compounds	Preliminary in vitro screening results, MIC (μg/mL)				Second level screening results, MIC (μg/mL)			
	MTB[a]	MS[b]	MF[c]	%[d]	MTB	MS	MF	MDR-TB
10a	1	1	10	90	1.25	1.25	1.25	>50
10b	1	10	10	95	0.625	10	10	6.25
10c	>100	10	>100	<90	5	–	–	>50
10d	>100	10	10	90	1.25	–	10	>50
10e	1	1	10	95	0.625	1.25	10	6.25
10f	>100	10	>100	<90	5	–	–	>50
10g	>100	>100	10	<90	10	10	10	>50
10h	1	1	10	90	0.625	1.25	10	6.25
10i	1	1	10	90	1.25	1.25	1.25	>50
10j	1	10	10	95	0.625	10	10	6.25
11a	10	10	>100	<90	5	10	–	25
11b	10	10	10	<90	2.5	10	10	>50
11c	>100	>100	>100	0	–	–	–	–
11d	10	>100	10	90	10	–	10	>50
11e	1	10	10	95	0.625	10	10	6.25
11f	>100	>100	>100	0	–	–	–	–
11g	10	>100	>100	<90	1.25	–	–	1.25
11h	>100	>100	>100	0	–	–	–	–
11i	10	10	>100	<90	2.5	2.5	–	2.5
11j	1	10	10	95	0.625	10	10	12.5
Isoniazid	0.7	50	12.5	95	0.7	50	12.5	12.5
Rifampicin	0.5	1.5	1.5	95	0.5	1.5	1.5	25

"–" Not detected

[a] *Mycobacterium tuberculosis* H37Rv

[b] *Mycobacterium smegmatis* (ATCC 19420)

[c] *Mycobacterium fortuitum* (ATCC 19542)

[d] Percentage of inhibition against *M. tuberculosis* H37Rv

which were active at 100 μg/mL concentration were not taken for further studies. The second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Amongst the tested compounds **10b**, **10e**, **10h**, **10j**, **11e**, and **11j** are active at 0.625 μg/mL concentrations against *M. tuberculosis* H37Rv strain and compounds **10a**, **10d**, **10i**, **11d**, and **11g** are active at 1.25 μg/mL concentrations. Similarly, the target molecules **10a**, **10e**, **10h**, and **10i** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420). It is interesting to note that most of the compounds showed either enhanced activity or activity in line with the reference compound isoniazid against *M. fortuitum* (ATCC 19542). Further, the compounds **10b**, **10e**, **10h**, **10j**, and **11e** showed promising activity against the MDR-TB strain at 6.25 μg/mL. These are just initial screening results to check the antimicrobial potential, since this is established and further work would be done to understand their mechanism of action.

Conclusion

We herein report the successful synthesis of (1*H*-indol-3-yl)alkyl-3-(1*H*-indol-3-yl)propanamide **10(a–j)** and **11(a–j)**. They have been characterized by spectral studies. All the title compounds have been investigated for their antimicrobial and antimycobacterial activities, the investigation of antibacterial and antifungal screening revealed that all the newly synthesizes compounds showed moderate to good inhibition at 1.56–25 μg/mL in DMSO. Compounds **10a**, **10b**, **10e**, **10h**, **10j**, **11b**, **11f**, **11i**, and **11j** exhibited comparatively good activity against the tested bacterial strains. Compounds **10a**, **10d**, **10j**, **11b**, and **11c** exhibited comparatively good activity against the five fungal strains. Further, the compounds **10b**, **10e**, **10h**, **10j**, and **11e** displayed significant activity against *M. tuberculosis* H37Rv strain. Furthermore, the target molecules **10a**, **10e**, **10h**, and **10i** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420). Similarly, the

compounds **10b**, **10e**, **10h**, **10j**, and **11e** showed substantial activity against the MDR-TB strain at 6.25 μg/mL. The halogen and trifluoro-substituted aromatic compounds will improve the lipophilic nature of the compound at the same time methyl-substituted compound would act as an electron donors. In addition, the presence of an amide group would be the essential element for hydrogen bonding with receptor. The above mentioned properties of these pharmacophores would be responsible for the promising activities of the title compounds. The scaffold synthesized in the research work can be taken for further derivatization in order to find the lead in these series.

Experimental

General

All reagents were purchased from Aldrich. Solvents used were extra dried. Final purifications were carried out using Quad biotage Flash purifier (A Dyax Corp. Company). Microwave-assisted syntheses were performed in Biotage initiator. TLC experiments were performed on alumina backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and molesybidinic acid. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.12 MHz) and AM-400 (400.13 MHz), Bruker Biospin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. Chemical shifts are reported in ppm (δ) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

General procedure for the preparation of compounds **2**(**a**–**e**)

5-Chloro indole-3-carboxaldehyde (5 g, 0.0278 mol) and hydroxylamine (2.9 g, 0.0417 mol) were dissolved in ethanol (200 mL) and stirred vigorously for 3 h at 60 °C. The reaction completion was monitored by TLC. After the completion, saturated Na_2CO_3 solution was added to bring the reaction mass to an alkaline medium. Concentrated the ethanol and the crude obtained were recrystalized in ethyl acetate/hexane. The yield of the compound obtained from this reaction is from 85 to 90 %. The spectral data of compounds **2**(**a**–**e**) are given below.

5-Chloro-1H-indole-3-carbaldehyde oxime

Appearance, off white solid (mp = 186–188 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 6.8 (s, 1H, CH), 7.1 (d, 1H, ArH), 7.38 (d, 1H, ArH), 7.46 (d, 1H, ArH), 7.6 (s, 1H, ArH), 9.1 (s, 1H, OH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 102.1, 112.9, 119.6, 121.9, 127.0, 127.5, 131.3, 133.9, 148.7; LC/MS (ESI–MS) m/z = 195.49 (M+1).

5-Chloro-2-methyl-1H-indole-3-carbaldehyde oxime

Appearance, pale yellow solid (mp = 192–194 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 3.2 (d, 3H, CH_3), 6.8 (s, 1H, CH), 6.83 (s, 1H, ArH), 7.21 (d, 1H, ArH), 7.28 (d, 1H, ArH), 7.29 (s, 1H, ArH), 9.1 (s, 1H, OH); ^{13}C δ ppm (DMSO, 400 MHz) = 42.3, 102.3, 112.9, 119.6, 121.9,126.8, 127.6, 134.4, 134.8, 148.1; LC/MS (ESI–MS) m/z = 209.72 (M+1).

5-Trifluoromethoxy-1H-indole-3-carbaldehyde oxime

Appearance, yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 6.78 (d, 1H, ArH), 6.80 (s, 1H, CH), 7.30 (s, 1H, ArH), 7.46 (d, 1H, ArH), 7.52 (d, 1H, ArH), 9.12 (S, 1H, OH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 102.1, 102.8, 109.6, 112.1, 121.8, 127.1, 127.8, 130.8, 148.2, 155.6; LC/MS (ESI–MS) m/z = 245.25 (M+1).

2-Methyl-5-trifluoromethoxy-1H-indole-3-carbaldehyde oxime

Appearance, white solid (mp = 197–199 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.38 (d, 3H, CH_3), 6.62 (S, 1H, ArH), 6.64 (d, 1H, ArH), 6.92 (S, 1H, CH), 7.12 (d, 1H, ArH), 11.26 (S, 1H, NH), 9.12 (S, 1H, OH); ^{13}C δ ppm (DMSO, 400 MHz) = 13.1, 102.6, 103.1, 109.8, 112.4, 122.2, 127.6, 127.82, 131.2, 149.4, 156.2; LC/MS (ESI–MS) m/z = 259.21 (M+1).

1,2-Dimethyl-5-trifluoromethoxy-1H-indole-3-carbaldehyde oxime

Appearance, semi solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.47 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.41 (s, 1H, ArH), 6.92 (d, 1H, ArH), 6.96 (d, 1H, ArH), 7.01 (s, 1H, CH), 9.34 (s, 1H, OH); ^{13}C δ ppm (DMSO, 400 MHz) = 7.6, 36.4, 104.1, 105.0, 110.6, 114.24, 123.2, 129.2, 130.4, 141.3, 149.7, 156.1; LC/MS (ESI–MS) m/z = 273.3 (M+1).

General procedure for the preparation of (1*H*-indol-3-yl)methanamine derivatives **3**(**a**–**e**)

The indole-3-methyloxime (4 g, 0.0205 mol) was dissolved in methanol (40 mL) and added ammonium hydroxide (8 mL), and raney nickel (5.9 g, 0.1025 mol), the reaction mass was stirred for 5 h at ambient

temperature. The reaction completion was monitored by TLC. After the completion, the reaction mass was filtered through Celite and concentrated the methanol, the crude product recrystalized in ethyl acetate/hexane. The spectral data of compounds **3**(**a**–**e**) are given below.

5-Chloro-1H-indole-3-methanamine

Appearance, colorless oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.9 (t, 2H, NH_2), 3.8 (t, 2H, CH_2), 6.8 (s, 1H, ArH), 7.1 (d, 1H, ArH), 7.2 (d, 1H, ArH), 7.2 (d, 1H, ArH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 45.6, 110.2, 110.2, 119.2, 121.4, 123.0, 127.7, 129.3, 134.5; LC/MS (ESI–MS) *m/z* = 181.2 (M+1). Anal. Calcd for C_9H_9ClN; C, 59.84; H, 5.02; N, 15.51; Found C, 59.98; H, 5.12; N, 15.58.

5-Chloro-1-methyl-1H-indole-3-methanamine

Appearance, off white solid (mp = 110–112 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.9 (t, 2H, NH_2), 3.8 (t, 2H, CH_2), 3.6 (d, 3H, CH_3), 6.4 (s, 1H, ArH), 6.7 (s, 1H, ArH), 6.9 (d, 1H, ArH), 7.3 (d, 1H, ArH); ^{13}C δ ppm (DMSO, 400 MHz) = 42.6, 46.9, 112.5, 112.5, 119.3, 121.87, 126.5, 126.7, 129.0, 135.9; LC/MS (ESI–MS) *m/z* = 195.6 (M+1). Anal. Calcd for $C_{10}H_{11}ClN_2$; C, 61.70; H, 5.7; N, 14.39; Found C, 61.98; H, 5.86; N, 14.83.

5-Trifluoromethoxy-1H-indole-3-methanamine

Appearance, white solid (mp = 156–158 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.9 (t, 2H, NH_2), 3.8 (t, 2H, CH_2), 6.8 (s, 1H, ArH), 7.1 (d, 1H, ArH), 6.7 (d, 1H, ArH), 6.7 (d, 1H, ArH), 10.0 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 46.5, 102, 112.0, 112.5, 120.0, 122.1, 122.2, 123.0, 128.6, 129.0; LC/MS (ESI–MS) *m/z* = 231.1 (M+1). Anal. Calcd for $C_{10}H_9F_3N_2O$; C, 52.18; H, 3.94; N, 12.17; Found C, 52.39; H, 4.02; N, 12.31.

2-Methyl-5-trifluoromethoxy-1H-indole-3-methanamine

Appearance, yellow liquid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.9 (t, 2H, NH_2), 2.2 (d, 3H, CH_3), 3.8 (t, 2H, CH_2), 6.3 (s, 1H, ArH), 6.7 (d, 1H, ArH), 6.74 (d, 1H, ArH), 11.26 (s, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 16.0, 43.5, 102.1, 109.5, 109.9, 112.3, 121.7, 128.4, 128.5, 131.4, 155.7; LC/MS (ESI–MS) *m/z* = 245.2 (M+1). Anal. Calcd for $C_{11}H_{11}F_3N_2O$; C, 54.10; H, 4.54; N, 11.47; Found C, 54.28; H, 4.62; N, 11.68.

1,2-Dimethyl-5-trifluoromethoxy-1H-indole-3-methanamine

Appearance, yellow solid (mp = 174–176 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.9 (t, 2H, NH_2), 2.4 (m, 3H, CH_3), 3.6 (m, 3H, CH_3), 3.8 (t, 2H, CH_2), 5.6 (s, 1H, ArH), 6.5 (d, 1H, ArH), 6.7 (d, 1H, ArH); ^{13}C δ ppm (DMSO, 400 MHz) = 13.0, 39.2, 43.8, 102.3, 109.6, 109.8, 112.6, 121.9, 128.6, 129.5, 132.6, 155.9; LC/MS (ESI–MS) *m/z* = 259.2 (M+1); Anal. Calcd for $C_{12}H_{13}F_3N_2O$; C, 55.81; H, 5.07; N, 10.85; Found C, 55.99; H, 5.28; N, 10.94.

General procedure for the preparation of compounds **4**(**a**–**e**)

5-Chloroindole-3-carboxaldehyde (5 g, 0.027 mol), cyanomethyltriphenyl phosphoniumbromide (21.82 g, 0.055 mol), and DBU (8.37 g, 0.055 mol) were dissolved in toluene (70 mL). The reaction mass was refluxed for 15 h at 110 °C. The reaction completion was monitored by TLC. After completion, charged (20 mL) of water and the product formed were extracted in ethylacetate. The organic layer was washed with water and was dried over sodium sulfate and concentrated under vacuum and the products obtained were purified by column chromatography on a silica gel (230–400 mesh) using ethyl acetate (20–40 %) in petroleum ether as eluant to afford **4a**–**4e**. The spectral data of compounds **4**(**a**–**e**) are given below.

3-(5-Chloro-1H-indole-3yl)acrylonitrile

Appearance, pale yellow solid (mp = 134–136 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 5.92 (d, 1H, CH), 7.02 (d, 1H, ArH), 7.14 (d, 1H, ArH), 7.28 (s, 1H, ArH), 7.42 (d, 1H, CH), 9.46 (d, 1H, ArH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 104.6, 111.2, 112.6, 118.4, 119.94, 122.4, 127.9, 128.4, 130.6, 133.9, 147.3; LC/MS (ESI–MS) *m/z* = 203.6 (M+1).

3-(5-Chloro-1-methyl-1H-indole-3yl)acrylonitrile

Appearance, yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 3.82 (d, 3H, CH_3), 5.92 (d, 1H, CH), 6.84 (s, 1H, ArH), 6.92 (d, 1H, ArH), 7.32 (d, 1H, ArH), 7.43 (d, 1H, CH), 8.97 (s, 1H, ArH); ^{13}C δ ppm (DMSO, 400 MHz) = 42.9, 104.6, 111.2, 112. 4, 118.4, 119.9, 122.4, 127.9, 128.4, 135.9, 136.2, 147.3; LC/MS (ESI–MS) *m/z* = 217.62 (M+1).

3-(5-(Trifluoromethoxy)-1H-indole-3yl)acrylonitrile

Appearance, semi solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 5.92 (d, 1H, CH), 6.64 (s, 1H, ArH), 6.54 (d, 1H, ArH), 6.73 (d, 1H, ArH), 7.42 (d, 1H, CH), 9.46 (d, 1H, ArH, 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 103.4, 104.6, 109.2, 110.2, 112.6, 118.3, 123.6, 128.4, 129.1, 131.2, 146.9, 156.5; LC/MS (ESI–MS) *m/z* = 253.31 (M+1).

3-(2-Methyl-5-(trifluoromethoxy)-1H-indole-3yl)acrylonitrile

Appearance, white solid (mp = 166–168 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.42 (d, 3H, CH_3), 5.92 (d, 1H, CH), 6.13 (s, 1H, ArH), 6.62 (d, 1H, ArH), 6.68 (d, 1H, ArH), 7.46 (d, 1H, CH), 11.26 (s, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 12.6, 103.4, 104.6, 109.24, 105.6, 112.6, 118.3, 123.6, 128.4, 129.1, 131.2, 146.9, 156.5; LC/MS (ESI–MS) *m/z* = 268.23 (M+1).

3-(1,2-Dimethyl-5-(trifluoromethoxy)-1H-indole-3yl)acrylonitrile

Appearance, white solid (mp = 172–174 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.42 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 5.92 (d, 1H, CH), 5.84 (s, 1H, ArH), 6.82 (d, 1H, ArH), 6.42 (d, 1H, ArH), 7.46 (d, 1H, CH); ^{13}C δ ppm (DMSO, 400 MHz) = 7.1, 37.2, 103.4, 104.6, 109.2, 105.6, 112.6, 118.3, 123.6, 129.2, 129.3, 141.4, 146.9, 156.5; LC/MS (ESI–MS) *m/z* = 283.31 (M+1).

General procedure for the preparation of 3-(1*H*-indol-3-yl)propan-1-amine derivatives **5**(**a**–**e**)

The above **4**(**a**–**e**) prepared compounds (3 g, 0.0148 mol) were dissolved in methanol (60 mL) and raney nickel (4.35 g, 0.074 mol) was added, and the reaction mass was stirred at 50 °C for 10 h under hydrogen atmosphere at 60 psi pressure. The reaction completion was monitored by TLC. After completion, the reaction mass was filtered through Celite. Concentrated the methanol and the crude obtained were purified by column chromatography on a silica gel (230–400 mesh) using ethyl acetate (40–50 %) in petroleum ether as eluant to afford **5**(**a**–**e**). The yield of the compound obtained from this reaction is from 40 to 50 %.

3-(5-Chloro-1H-indol-3-yl)propane-1-amine

Appearance, brown oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.91 (m, 2H, CH_2), 2.12 (t, 2H, NH_2), 2.53 (t, 2H, CH_2), 2.74 (m, 2H, CH_2), 6.92 (d, 1H, ArH), 7.20 (d, 1H, ArH), 7.28 (d, 1H, ArH), 7.32 (s, 1H, ArH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.9, 33.6, 42.6, 111.8, 113.1, 120.1, 122.1, 123.1, 126.9, 129.1, 135.3; LC/MS (ESI–MS) *m/z* = 209.68 (M+1); Anal. Calcd for $C_{11}H_{13}ClN_2$; C, 63.31; H, 6.28; N, 13.42; Found C, 63.39; H, 6.32; N, 13.49.

3-(5-Chloro-1-methyl-1H-indol-3-yl)propane-1-amine

Appearance, brown oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.91 (m, 2H, CH_2), 2.12 (t, 2H, NH_2), 2.53 (t, 2H, CH_2), 2.74 (m, 2H, CH_2), 3.84 (d, 3H, CH_3), 6.55 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.90 (d, 1H, ArH), 7.34 (d, 1H, ArH), ^{13}C δ ppm (DMSO, 400 MHz) = 28.2, 33.6, 42.6, 43.6, 112.4, 113.4, 120.1, 123.1, 126.9, 127.4, 129.1, 136.8; LC/MS(ESI–MS) *m/z* = 223.9 (M+1); Anal. Calcd for $C_{12}H_{15}ClN_2$; C, 64.71; H, 6.79; N, 12.58; Found C, 64.77; H, 6.82; N, 12.64.

3-(5-(Trifluoromethoxy)-1H-indol-3-yl)propane-1-amine

Appearance, yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.91 (m, 2H, CH_2), 2.12 (t, 2H, NH_2), 2.53 (t, 2H, CH_2), 2.74 (m, 2H, CH_2), 6.92 (d, 1H, ArH), 6.72 (s, 1H, ArH), 6.81 (d, 1H, ArH), 7.24 (d, 1H, ArH), 11.26 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 28.2, 33.6, 42.6, 103.4, 110.1, 111.2, 113.2, 122.6, 123.6, 129.8, 129.9, 156.3; LC/MS (ESI–MS) *m/z* = 259.29; Anal. Calcd for $C_{12}H_{13}F_3N_2O$; C, 55.81; H, 5.07; N, 10.85; Found C, 55.92; H, 5.13; N, 10.81.

3-(2-Methyl-5-(trifluoromethoxy)-1H-indol-3-yl)propane-1-amine

Appearance, semi solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.91 (m, 2H, CH_2), 2.12 (t, 2H, NH_2), 2.42 (d, 3H, CH_3), 2.53 (t, 2H, CH_2), 2.74 (m, 2H, CH_2), 6.31 (s, 1H, ArH), 6.76 (d, 1H, ArH), 6.94 (d, 1H, ArH), 11.26 (s, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 12.6, 21.2, 33.6, 42.1, 103.1, 109.6, 110.1, 113.4, 122.1, 129.6, 129.9, 132.4, 156.5; LC/MS (ESI–MS) *m/z* = 273.27 (M+1); Anal. Calcd for $C_{13}H_{15}F_3N_2O$; C, 57.35; H, 5.55; N, 10.29; Found C, 57.42; H, 5.59; N, 10.26.

3-(1,2-Dimethyl-5-(trifluoromethoxy)-1H-indol-3-yl)propane-1-amine

Appearance, semi solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.91 (m, 2H, CH_2), 2.12 (t, 2H, NH_2), 2.42 (d, 3H, CH_3), 2.53 (t, 2H, CH_2), 2.74 (m, 2H, CH_2), 3.84 (s, 3H, CH_3), 5.92 (s, 1H, ArH), 6.62 (d, 1H, ArH), 6.92 (d, 1H, ArH); ^{13}C δ ppm (DMSO, 400 MHz) = 6.0, 21.2, 34.3, 36.2, 42.6, 102.4, 109.1, 110.6, 113.4, 122.9, 129.7, 130.6, 134.1, 156.4; LC/MS (ESI–MS) *m/z* = 287.32; Anal. Calcd for $C_{14}H_{17}F_3N_2O$; C, 58.73; H, 5.99; N, 9.78; Found C, 58.82; H, 6.03; N, 9.81.

Procedure for the preparation of ethyl-3-(5-chloro-1*H*-indol-3-yl)acrylate (**6**)

5-Chloro indole-3-carboxaldehyde (20 g, 0.0278 mol) and ethoxycarbonylmethyl triphenylphosphoniumbromide (95.6 g 0.222 mol), and DBU (33.8 g, 0.222 mol) were dissolved in toluene (300 mL) and refluxed at 120 °C for 20 h. The reaction was monitored by TLC. After completion, toluene was concentrated under vacuum. Crude obtained was purified by column chromatography on a silica gel (230–400 mesh)

using ethyl acetate (10–20 %) in petroleum ether as eluant to afford **9** as an off white solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.42 (t, 3H, CH_3), 4.23 (m, 2H, CH_2), 6.42 (d, 1H, CH), 6.99 (d, 1H, ArH), 7.22 (d, 1H, ArH), 7.28 (s, 1H, ArH), 7.82 (d, 1H, CH), 9.43 (d, 1H, ArH), 11.26 (d, 1H, NH).

Procedure for the preparation of ethyl 3-(5-chloro-1*H*-indol-3-yl)propanoate (**7**)

Ethyl-3-(5-chloro-1*H*-indol-3-yl)acrylate (3 g, 0.012 mol) and PtO_2 (2.7 g, 0.012 mol) were dissolved in methanol (30 mL) and stirred under hydrogen atmosphere for 12 h. The reaction was monitored by TLC. After completion, methanol was concentrated under vacuum. Crude obtained was purified by column chromatography on a silica gel (230–400 mesh) using ethyl acetate (10–20 %) in petroleum ether as eluant to afford **10** as an off white solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.42 (t, 3H, CH_3), 2.67 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 4.22 (m, 2H, CH_2), 6.94 (d, 1H, ArH), 7.21 (d, 1H, ArH), 7.32 (d, 1H, ArH), 7.34 (s, 1H, ArH), 11.26 (d, 1H, NH).

General procedure for the preparation of ethyl 3-(5-chloro-1*H*-indol-3-yl)acrylate derivatives **8**(**a**, **b**)

5-Chloro indole-3-carboxaldehyde (5 g, 0.027 mol) and malonic acid (3.18 g, 0.031 mol) were dissolved in pyridine (50 mL) and piperidine (5 mL). The reaction mixture was heated at 115 °C for 14 h. The reaction was monitored by TLC. After completion, the reaction mixture was extracted with ethyl acetate (50 mL), the organic layer was separated and concentrated under reduced pressure to afford **8**(**a**, **b**). The spectral data of compounds **8**(**a**, **b**) are given below.

*3-(5-Chloro-1H-indole-3yl)acrylicacid (**8a**)*

Appearance, off white solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 6.52 (d, 1H, CH), 6.98 (d, 1H, ArH), 7.24 (d, 1H, ArH), 7.28 (s, 1H, ArH), 7.81 (d, 1H, CH), 9.42 (d, 1H, ArH), 10.46 (d, 1H, NH), 12.01 (s, 1H, COOH).

*3-(5-Chloro-1-methyl-1H-indole-3yl)acrylicacid (**8b**)*

Appearance, off white solid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 3.42 (s, 3H, CH_3), 6.52 (d, 1H, CH), 6.86 (d, 1H, ArH), 7.18 (d, 1H, ArH), 7.22 (s, 1H, ArH), 7.69 (d, 1H, CH), 8.97 (s, 1H, ArH), 12.01 (s, 1H, COOH).

General procedure for the preparation of ethyl 3-(5-chloro-1*H*-indol-3-yl)propanoate derivatives **9**(**a**, **b**)

Ethyl-3-(5-chloro-1*H*-indol-3-yl)acrylic acid (3 g, 0.013 mol) and PtO_2 (3.07 g, 0.013 mol) were dissolved in methanol (30 mL) and stirred under hydrogen atmosphere for 8 h. The reaction was monitored by TLC. After the completion, methanol was concentrated under vacuum. Crude obtained was purified by column chromatography on a silica gel (230–400 mesh) using ethyl acetate (40–50 %) in petroleum ether as eluant to afford **9**(**a**, **b**).

*3-(5-Chloro-1H-indol-3yl)propanoic acid (**9a**)*

Appearance, colorless liquid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.59 (t, 2H, CH_2), 2.92 (t, 2H, CH_2), 6.92 (d, 1H, ArH), 7.21 (d, 1H, ArH), 7.26 (d, 1H, ArH), 7.28 (s, 1H, ArH), 10.46 (d, 1H, NH), 11.96 (s, 1H, COOH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.8, 39.2, 111.2, 113.6, 119.8, 122.3, 123.9, 127.3, 129.2, 135.4, 178.2; LC/MS (ESI–MS) *m/z* = 224.69 (M+1); Anal. Calcd for C11H10ClNO2; C, 59.07; H, 4.51; N, 6.26; Found C, 59.11; H, 4.53; N, 6.64.

*3-(5-Chloro-1-methyl-1H-indol-3yl)propanoic acid (**9b**)*

Appearance, white solid (mp = 180–082 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.48 (t, 2H, CH_2), 2.69 (t, 2H, CH_2), 3.68 (s, 3H, CH_3), 6.48 (s, 1H, ArH), 6.97 (s, 1H, ArH), 7.01 (d, 1H, ArH), 7.08 (d, 1H, ArH), 11.96 (s, 1H, COOH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.3, 36.4, 43.4, 111.4, 112.6, 120.1, 122.4, 125.9, 126.8, 130.2, 136.3, 176.6; LC/MS (ESI–MS) *m/z* = 238.69 (M+1); Anal. Calcd for $C_{12}H_{12}ClNO_2$; C, 60.64; H, 5.09; N, 5.89; Found C, 60.68; H, 5.11; N, 5.92.

General procedure for the preparation of compounds **10**(**a–j**) and **11**(**a–j**)

A mixture of 3-(5-chloro-1*H*-indol-3-yl)propanoic acid (0.5 g, 0.0022 mol), EDCl (0.0034 mol), HOBT (0.022 mol), triethylamine (0.93 mL, 0.0066 mol), and dichloromethane (5.0 mL) were stirred vigorously for 10 min at 25 °C. Then amine (0.0022 mol) in dichloromethane was added slowly to the reaction mixture. The reaction mass was stirred at 25 °C for 3 h. The reaction completion was monitored by TLC. After completion, the reaction mass was diluted with dichloromethane, washed with 10 % $NaHCO_3$ (10 mL), brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using ethyl acetate:petroleum ether (3:1) as eluant to methanol:methylene chloride (2–6 %). The spectral data of compounds **10**(**a–j**) and **11**(**a–j**) are given below.

*3-(5-Chloro-1H-indol-3-yl)-N-((5-(trifluoromethoxy)-1H-indol-3-yl)methyl)propanamide (**10a**)*

Appearance, white solid (mp = 213–215 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.45 (t, 2H, CH_2), 2.71

(t, 2H, CH_2), 4.34 (d, 2H, CH_2), 6.69 (s, 1H, ArH), 6.80 (d, 2H, ArH), 7.12 (d, 1H, ArH), 7.20 (m, 4H, ArH), 9.2 (t, 1H, NH), 10.32 (d, 2H, NH); ^{13}C NMR (DMSO, 400 MHz) δ ppm = 27.4, 36.1, 36.4, 103.7, 108.6, 110.9, 111.2, 112.8, 118.3, 120.8, 122.1, 125.8, 128.5, 129.2, 134.2, 152.3, 172.1; LC/MS (ESI–MS) m/z = 436.9 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-((2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl) methyl) propanamide (**10b**)*

Appearance, brown oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.11 (s, 3H, CH_3), 2.45 (t, 2H, CH_2), 2.71 (t, 2H, CH_2), 4.34 (d, 2H, CH_2), 6.69 (s, 1H, ArH), 6.80 (d, 2H, ArH), 7.12 (d, 1H, ArH), 7.20 (m, 4H, ArH), 9.2 (t, 1H, NH), 10.30 (s, 1H, NH), 10.32 (d, 1H, NH); ^{13}C NMR (DMSO, 400 MHz) δ ppm = 12.6, 27.4, 36.1, 36.4, 103.7, 108.6, 110.9, 111.2, 112.8, 118.3, 120.8, 122.1, 125.8, 128.5, 129.2, 131.3, 134.2, 152.3, 172.1; LC/MS (ESI–MS) m/z = 450.91 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-((1,2-dimethyl-5-(trifluoromethoxy)-1H-indol-3-yl) methyl) propanamide (**10c**)*

Appearance, off white solid (mp = 261–263 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.11 (s, 3H, CH_3), 2.45 (t, 2H, CH_2), 2.71 (t, 2H, CH_2), 3.64 (s, 3H, CH_3), 4.34 (d, 2H, CH_2), 5.84 (s, 1H, ArH), 6.52 (d, 1H, ArH), 6.81 (d, 2H, ArH), 7.22 (m, 3H, ArH), 9.24 (t, 1H, NH), 10.30 (d, 1H, NH), 10.32 (d, 1H, NH); ^{13}C NMR (DMSO, 400 MHz) δ ppm = 5.6, 28.1, 31.6, 36.1, 36.4, 103.7, 108.6, 110.9, 111.2, 112.8, 118.3, 120.8, 122.1, 122.9, 125.8, 128.5, 129.2, 131.3, 134.2, 152.3, 172.1, LC/MS (ESI–MS) m/z = 464.7 (M+1).

*N-((5-Chloro-1-methyl-1H-indol-3-yl)methyl)-3-(5-chloro-1H-indol-3yl)propanamide (**10d**)*

Appearance, white solid (mp = 209–211 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.45 (t, 2H, CH_2), 2.71 (t, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 6.41 (s, 1H, ArH), 6.83 (s, 1H, ArH), 6.89 (d, 1H, ArH), 7.11 (d, 1H, ArH), 7.21 (m, 3H, ArH), 7.29 (d, 1H, ArH), 9.16 (t, 1H, NH), 10.32 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 28.1, 36.8, 38.1, 42.4, 110.9, 112.5, 119.3, 121.6, 122.9, 126.5, 126.9, 128.9, 129.2, 134.6, 135.7, 173.7; LC/MS (ESI–MS) m/z = 401.1 (M+1).

3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-((5-(trifluoromethoxy)-1H-indol-3-yl) methyl) propanamide (10e)

Appearance, brown solid (mp = 235–237 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.45 (t, 2H, CH_2), 2.71 (t, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.40 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.81 (d, 1H, ArH), 6.88 (s, 2H, ArH), 6.91 (d, 1H, ArH), 7.12 (d, 1H, ArH), 7.31 (d, 1H, ArH), 9.23 (t, 1H, NH), 10.32 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 27.4, 36.1, 36.4, 42.4, 103.7, 108.6, 110.9, 111.2, 112.8, 118.3, 120.8, 122.1, 124.9, 125.8, 128.0, 128.5, 129.2, 134.2, 152.3, 172.1; LC/MS (ESI–MS) m/z = 450.8 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-((1,2-dimethyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)propanamide (**10f**)*

Appearance, brown semisolid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.31 (s, 3H, CH_3), 2.48 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 3.61 (s, 6H, CH_3), 4.38 (d, 2H, CH_2), 5.87 (s, 1H, ArH), 6.38 (s, 1H, ArH), 6.54 (d, 1H, ArH), 6.80 (d, 1H, ArH), 6.84 (s, 1H, ArH), 6.88 (d, 1H, ArH), 7.34 (d, 1H, ArH), 9.21 (t, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = = 5.6, 28.1, 31.6, 35.8, 36.4, 42.4, 103.7, 108.6, 110.9, 111.2, 112.0, 112.8, 118.3, 120.8, 122.1, 125.8, 126.4, 128.5, 129.2, 131.3, 134.2, 152.3, 172.1; LC/MS (ESI–MS) m/z = 479.2 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-((5-chloro-1-methyl-1H-indol-3-yl) methyl)propanamide (**10g**)*

Appearance, brown solid (mp = 254–256 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.48 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 3.61 (s, 6H, CH_3), 4.38 (d, 2H, CH_2), 6.34 (s, 2H, ArH), 6.82 (s, 2H, ArH), 6.89 (d, 2H, ArH), 7.28 (d, 2H, ArH), 9.24 (t, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 28.4, 36.8, 38.1, 42.4, 111.2, 112.5, 119.3, 121.6, 126.5, 126.8, 129.2, 135.7, 173.7; LC/MS (ESI–MS) m/z = 415.2 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-((5-chloro-1H-indol-3-yl)methyl)propanamide (**10h**)*

Appearance, White solid (mp = 219–221 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.48 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 4.38 (d, 2H, CH_2), 6.82 (d, 2H, ArH), 7.10 (d, 2H, ArH), 7.18 (m, 2H, ArH), 7.20 (d, 2H, ArH), 9.24 (t, 1H, NH), 10.34 (d, 2H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 28.1, 36.8, 37.6, 110.9, 112.1, 112.6, 119.3, 121.6, 122.9, 126.5, 129.2, 134.7, 173.7; LC/MS (ESI–MS) m/z = 388.1 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-((2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl) methyl)propanamide (**10i**)*

Appearance, pale yellow liquid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.32 (s, 3H, CH_3), 2.48 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.38 (d, 2H, CH_2), 6.22

(s, 1H, ArH), 6.38 (s, 1H, ArH), 6.89 (d, 3H, ArH), 7.10 (s, 1H, ArH), 7.28 (d, 1H, ArH), 9.21 (t, 1H, NH), 10.32 (s, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 12.1, 28.4, 31.3, 36.8, 42.4, 102.1, 109.1, 109.6, 111.2, 112.0, 112.6, 119.3, 121.3, 121.9, 126.3, 126.8, 128.5, 129.2, 131.3, 135.7, 155.6, 173.7; LC/MS (ESI–MS) m/z = 465.2 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-((5-chloro-1H-indol-3-yl)methyl)propanamide (**10j**)*

Appearance- White solid (mp = 208–210 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.48 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.38 (d, 2H, CH_2), 6.38 (s, 1H, ArH), 6.80 (s, 1H, ArH), 6.82 (d, 1H, ArH), 6.89 (d, 1H, ArH), 7.19 (d, 2H, ArH), 7.24 (s, 1H, ArH), 7.28 (d, 1H, ArH), 9.22 (t, 1H, NH), 10.32 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 28.4, 36.8, 37.8, 42.4, 111.2, 112.1, 112.6, 119.3, 121.6, 122.9, 126.5, 126.8, 128.9, 129.4, 134.6, 135.7, 173.7; LC/MS (ESI–MS) m/z = 401.4 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-(3-(5-chloro-1-methyl-1H-indol-3-yl) propyl)propanamide (**11a**)*

Appearance, off white solid (mp = 249–251 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.48 (t, 4H, CH_2), 2.78 (t, 2H, CH_2), 3.26 (m, 2H, CH_2), 3.68 (s, 6H, CH_3), 6.48 (s, 2H, ArH), 6.92 (s, 2H, ArH), 7.06 (d, 2H, ArH), 7.41 (d, 2H, ArH), 9.28 (t, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 27.1, 28.4, 30.2, 36.8, 39.2, 42.4, 111.2, 112.5, 119.3, 121.6, 126.2, 126.8, 129.2, 135.7, 172.8; LC/MS (ESI–MS) m/z = 443.5 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-(3-(2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl) propyl) propanamide (**11b**)*

Appearance, off white solid (mp = 283–285 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.48 (t, 4H, CH_2), 2.68 (t, 2H, CH_2), 3.24 (m, 2H, CH_2), 6.28 (s, 1H, ArH), 6.76 (d, 2H, ArH), 6.84 (d, 1H, ArH), 7.21 (d, 2H, ArH), 7.24 (s, 1H, ArH), 9.26 (t, 1H, NH), 10.34 (s, 1H, NH), 10.36 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 12.4, 20.3, 28.1, 30.5, 36.8, 39.2, 102.1, 108.4, 109.4, 110.5, 112.0, 112.5, 119.3, 121.1, 121.7, 122.9, 126.8, 128.2, 128.7, 129.4, 131.3, 134.6, 155.6, 172.8; LC/MS (ESI–MS) m/z = 479.2 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-(3-(5-chloro-1H-indol-3-yl)propyl)propanamide (**11c**)*

Appearance, brown solid (mp = 264–266 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 2.02 (m, 2H, CH_2), 2.21 (t, 4H, CH_2), 2.48 (t, 2H, CH_2), 3.42 (d, 2H, CH_2), 6.88 (s, 2H, ArH), 7.21 (m, 4H, ArH), 7.28 (s, 2H, ArH), 9.20 (t, 1H, NH), 10.32 (d, 2H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.8, 28.1, 30.2, 36.8, 39.2, 110.9, 112.5, 119.3, 121.6, 122.9, 126.8, 128.9, 134.6, 172.8; LC/MS (ESI–MS) m/z = 416.1 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-(3-(1,2-dimethyl-5-(trifluoromethoxy)-1H-indol-3-yl)propyl) propanamide (**11d**)*

Appearance, semisolid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.48 (t, 4H, CH_2), 2.69 (t, 2H, CH_2), 3.34 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 6.02 (s, 1H, ArH), 6.48 (d, 1H, ArH), 6.81 (d, 1H, ArH), 6.84 (d, 1H, ArH), 7.22 (d, 2H, ArH), 7.26 (s, 1H, ArH), 9.26 (t, 1H, NH), 10.34 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 5.9, 20.6, 28.1, 30.5, 35.9, 36.8, 39.2, 102.1, 108.6, 109.6, 110.9, 112.1, 112.5, 119.3, 121.1, 121.9, 122.9, 126.8, 128.3, 128.9, 129.7, 132.6, 134.6, 154.8, 172.8; LC/MS (ESI–MS) m/z = 493.1 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-(3-(5-(trifluoromethoxy)-1H-indol-3-yl)propyl) propanamide (**11e**)*

Appearance, semisolid; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.48 (t, 4H, CH_2), 2.70 (t, 2H, CH_2), 3.28 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 6.38 (s, 1H, ArH), 6.72 (d, 1H, ArH), 6.78 (s, 1H, ArH), 6.82 (d, 1H, ArH), 6.88 (s, 1H, ArH), 7.28 (d, 3H, ArH), 9.24 (t, 1H, NH), 10.35 (s, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.8, 28.4, 30.2, 36.8, 39.2, 42.4, 102.1, 109.6, 112.0, 112.6, 119.3, 121.3, 121.8, 122.9, 126.1, 126.7, 128.2, 128.9, 129.6, 135.7, 155.6, 172.8; LC/MS (ESI–MS) m/z = 479.1 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-(3-(5-(trifluoromethoxy)-1H-indol-3-yl) propyl)propanamide (**11f**)*

Appearance, white solid (mp = 254–256 °C); ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.48 (t, 4H, CH_2), 2.70 (t, 2H, CH_2), 3.28 (m, 2H, CH_2), 6.72 (d, 1H, ArH), 6.76 (s, 1H, ArH), 6.82 (d, 1H, ArH), 6.88 (s, 1H, ArH), 7.27 (d, 3H, ArH), 7.29 (s, 1H, ArH), 9.24 (t, 1H, NH), 10.34 (d, 2H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.8, 28.1, 30.2, 36.8, 39.2, 102.1, 109.6, 110.9, 112.1, 112.9, 119.3, 121.5, 121.9, 122.8, 126.8, 128.2, 128.7, 129.4, 134.6, 154.8, 172.8; LC/MS (ESI–MS) m/z = 464.9 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-(3-(1,2-dimethyl-5-(trifluoromethoxy)-1H-indol-3-yl)propyl)propanamide (**11g**)*

Appearance, yellow oil; ^{1}H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.48 (t, 4H,

CH_2), 2.76 (t, 2H, CH_2), 3.24 (m, 2H, CH_2), 3.64 (s, 6H, CH_3), 5.87 (s, 1H, ArH), 6.38 (s, 1H, ArH), 6.54 (d, 1H, ArH), 6.76 (d, 1H, ArH), 6.84 (s, 1H, ArH), 6.92 (d, 1H, ArH), 7.32 (d, 1H, ArH), 9.26 (t, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 5.9, 20.6, 28.4, 30.5, 35.9, 36.8, 39.2, 42.4, 102.1, 108.6, 109.5, 112.2, 112.1, 112.5, 119.3, 121.4, 121.9, 126.4, 126.8, 128.7, 129.1, 129.6, 132.6, 135.7, 154.9, 172.6; LC/MS (ESI–MS) m/z = 506.8 (M+1).

*N-(3-(5-Chloro-1-methyl-1H-indol-3-yl)propyl)-3-(5-chloro-1H-indol-3-yl)propanamide (**11h**)*

Appearance, white solid (mp = 238–240 °C); ^1H NMR (DMSO, 400 MHz) δ ppm = 1.89 (m, 2H, CH_2), 2.21 (t, 4H, CH_2), 2.48 (t, 2H, CH_2), 3.42 (d, 2H, CH_2), 3.66 (s, 3H, CH_3), 6.35 (s, 1H, ArH), 6.82 (d, 1H, ArH), 6.84 (s, 1H, ArH), 6.92 (d, 1H, ArH), 7.18 (d, 3H, ArH), 7.29 (d, 1H, ArH), 9.21 (t, 1H, NH), 10.32 (d, 2H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 27.1, 28.1, 30.2, 36.8, 39.2, 42.4, 110.9, 111.2, 112.5, 119.3, 121.6, 122.9, 126.5, 126.8, 128.9, 129.4, 134.6, 135.7, 172.9; LC/MS (ESI–MS) m/z = 429.5 (M+1).

*3-(5-Chloro-1-methyl-1H-indol-3-yl)-N-(3-(5-chloro-1H-indol-3-yl)propyl)propanamide (**11i**)*

Appearance, off white solid (mp = 241–243 °C); ^1H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.46 (t, 4H, CH_2), 2.70 (t, 2H, CH_2), 3.36 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 6.38 (s, 1H, ArH), 6.72 (d, 1H, ArH), 6.82 (s, 1H, ArH), 6.90 (d, 1H, ArH), 7.16 (d, 2H, ArH), 7.25 (s, 1H, ArH), 7.32 (d, 1H, ArH), 9.21 (t, 1H, NH), 10.34 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 26.8, 28.4, 30.2, 36.8, 39.4, 42.4, 110.9, 111.2, 112.5, 119.3, 121.6, 122.9, 126.5, 126.9, 128.8, 129.6, 134.6, 135.7, 172.9; LC/MS (ESI–MS) m/z = 429.5 (M+1).

*3-(5-Chloro-1H-indol-3-yl)-N-(3-(2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)propyl) propanamide (**11j**)*

Appearance, semi solid; ^1H NMR (DMSO, 400 MHz) δ ppm = 1.86 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.48 (t, 4H, CH_2), 2.72 (t, 2H, CH_2), 3.26 (m, 2H, CH_2), 6.26 (s, 1H, ArH), 6.72 (d, 2H, ArH), 6.81 (d, 1H, ArH), 7.14 (d, 1H, ArH), 7.20 (d, 1H, ArH), 7.22 (s, 1H, ArH), 9.22 (t, 1H, NH), 10.32 (s, 1H, NH), 10.36 (d, 1H, NH); ^{13}C δ ppm (DMSO, 400 MHz) = 12.6, 20.6, 28.4, 30.4, 36.8, 39.7, 102.1, 108.3, 109.6, 110.9, 112.1, 112.6, 119.3, 121.4, 121.8, 122.9, 126.8, 128.0, 128.5, 128.9, 131.3, 134.6, 154.8, 172.8; LC/MS (ESI–MS) m/z = 479.1 (M+1).

Antibacterial studies

The synthesized compounds were screened for their antibacterial activity against *E. coli* (ATCC 25922), *S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853), and *K. pneumoniae* (recultured), and *S. pyogenes* bacterial strains by serial plate dilution method (Barry, 1980). Serial dilutions of the drug in Mueller–Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial disks are placed on the agar for the sole purpose of producing zone of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using an agar punch, wells were made on these seeded agar plates and MIC of the test compounds in dimethylsulfoxide (DMSO, 400 MHz) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antibacterial activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with ciprofloxacin as standard. MIC (μg/mL) and zone of inhibition (mm) were determined for all the synthesized compounds and the corresponding results are summarized in Table 2.

Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *A. flavus* (NCIM No. 524), *Aspergillus fumigarus* (NCIM No. 902), *P. marneffei* (recultured), and *T. mentagrophytes* (recultured), and *C. albicans* in DMSO by serial plate dilution method (Verma *et al*., 1998). Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal stain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates MICs of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition

zone. Activity of each compound was compared with Ciclopirox olamine as standard. MIC (μg/mL) and zone of inhibition (mm) were determined for all the synthesized compounds and their corresponding results are summarized in Table 3.

Antituberculosis studies

The compounds were screened for their in vitro antimycobacterial activity against *M. Tuberculosis* H37Rv ATCC 27294 and non-tubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420, and *M. fortuitum* ATCC 19542 by resazurin assay method (Neetu and Jaya, 2007) and their MIC values were determined. The standard drugs, viz. isoniazid and rifampicin were used for comparison. *M. tuberculosis* strains were grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10 % OADC Becton–Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 2 standard with the same medium. From this, 50 μL of this culture was added to 150 μL of fresh medium in 96-well microtitre plates. Stock solutions (2 mg/mL) of the test compounds were prepared in dimethyl formamide (DMF). The compounds were tested at 1, 10, and 100 μg/mL concentrations. Further, the second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Control tubes had the same volumes of DMF without any substrate. Rifampicin and isoniazid were used as the reference compounds. After incubation at 37 °C for 7 days, 20 μL of 0.01 % resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a color change from blue to pink after 1 h at 37 °C. Compounds which prevented the change of color of the dye were considered to be inhibitory to *M. tuberculosis*.

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