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FULL-LENGTH PAPER

Synthesis of novel spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazoles via a regioselective three-component [3+2] cycloaddition and their preliminary antimicrobial evaluation

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Abstract A series of spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazoles hybrid compounds were prepared in good yields by regioselective, three-component, 1,3-dipolar cycloaddition reactions between α, β-unsaturated ketones with furanyl substituents and unstable azomethine ylides, which were generated in situ from isatin and various types of amino acids. The synthesized compounds were screened for their antibacterial activities against a spectrum of pathogens. Preliminary studies identified compound **5c** as a potent antimicrobial agent against drug-resistant bacteria. In addition, molecular docking studies indicated that compound **5c** showed strong interactions with the active sites of lanosterol demethylase, dihydrofolate reductase, and topoisomerase II. This study provides an effective entry to the rapidly construction of a chemical library of heterocycles and compound **5c** is one potent antibacterial lead for subsequent optimization.

Keywords 1,3-Dipolar cycloaddition · Azomethine ylides · Antibacterial · Multi-component reactions (MCRs) · Spirooxindole derivatives

Introduction

Spirooxindoles, such as functionalized spirooxindolo-pyrrolidine and pyrrolizidine, are important structural building blocks found in many natural products and they represent attractive targets in organic synthesis because of their highly pronounced biological properties as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals [1–3]. Spirooxindoles have been reported to exhibit biological activities such as antimicrobial [4], antitumoral [5], anti-inflammatory [6], anti-HIV [7] and potent non-peptide inhibition of the p53–MDM2 interaction [8,9]. For instance, compound **1a**, coerulescine, the simplest spirooxindole–pyrrolidine alkaloid in nature, displays a local anesthetic effect [10]; compound **1b**, spirotryprostatin A, isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly and serotonin receptor inhibitor [11]; compound **2a**, pteropodine and its analog compound **2b**, rychnophylline are in advanced preclinical development for antigenotoxic, antioxidant therapeutics [12] (Fig. 1).

Although numerous impressive successes have been recorded for the synthesis of diversely structured spirooxindoles over the past years, the conventional one-pot, multi-component reactions are one of the most significant strategies for the synthesis [13–19]. In this regard, 1,3-dipolar cycloaddition could provide an efficient approach for the construction of nitrogen-containing five-membered ring heterocycles [20,21]. At the same time, many research groups

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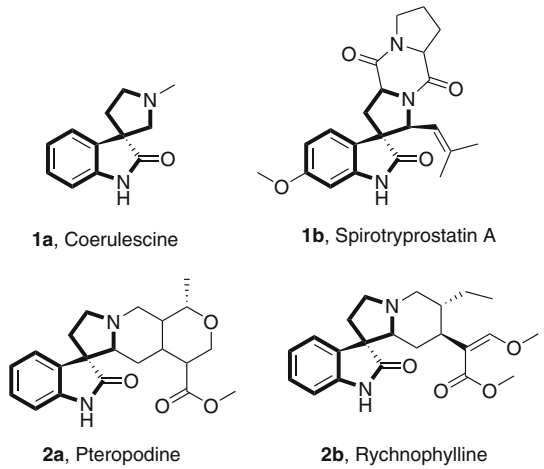


Fig. 1 Representative bioactive small-molecule natural products having a spirooxindolo- pyrrolidine building block

worked on the application of multi-component, domino 1,3-dipolar cycloaddition reactions to constitute a versatile protocol for the construction of poly functionalized spiro-heterocycles viz. spiro-pyrrolidines and pyrrolizines, and their screening for antimicrobial activity. Some institutions and companies have unearthed several compounds with activities comparable to or superior to some of the currently employed first-line antibacterial drugs [22–30]. After large-scale synthesis, the preliminary results exhibited that screening hit compounds generally had different heterocyclic functional groups, such as nitrophenyl [23], beta-lactam [24], and thiophene [28]. Among them, the furanyl group was an active moiety present in widely used antibiotics such as furazolidone, furacilin, and nitrofurantoin, which were also used as chemotherapeutic agents for treating microbial diseases. Hence, there is a renewed interest in the synthesis of furanyl-containing spirooxindoles with potential antibacterial applications.

Prompted by these considerations and as a part of our own interest in cycloaddition reactions, we report herein the preliminary studies about the efficient synthesis of novel regiosteselective spiropyrrolidine pyrrolidines, pyrrolizidines, and pyrrolothiazole frameworks containing a furanyl moiety via the one-pot, multicomponent condensation of azomethine ylides (generated in situ from amino acids and isatin) with the Knoevenagel adduct derivatives (preformed from the reaction of 2-acetyl furan with substituted benzaldehydes). A library of compounds with spirooxindole structures was synthesized and screened for potential antimicrobial activities. This study formed a part of our researches initiated on the construction of novel heterocycles via 1,3-dipolar cycloaddition reactions to discover new lead compounds with antibacterial activities.

Results and discussions

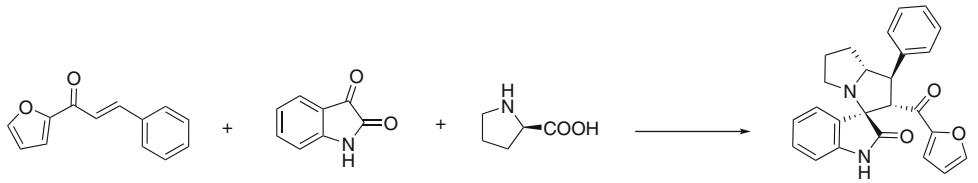
In our initial endeavour, the Knoevenagel adducts **3a**–**g** were synthesized via a classic conventional method by condensing commercially available 2-acetyl furan and substituted benzaldehydes in ethanol using NaOH as catalyst. Crude intermediates were purified by recrystallization in ethanol with 63–99 % total yields. Melting point, NMR and mass spectrometry data were consistent with those reported in the literature [31,32].

From a mechanistic perspective and in combination with our experience in this field, we envisaged that an azomethine ylide could be generated in situ from isatin and L-proline, then trapped with 3-phenyl-1-(furan-2-yl)prop-2-enone (**3d**) acting as dipolarophile to afford spiropyrrolizidine oxindole **5d**. Therefore, we started our investigation using a one-pot multicomponent synthesis with isatin, L-proline, and 3-phenyl-1-(furan-2-yl) prop-2-enone (**3d**) as a model reaction.

The reaction parameters including solvents and reaction temperatures were preliminary screened. Several solvents including 1,4-dioxane, THF, toluene, CH_3CN, CH_3OH, EtOH and H_2O were explored (Table 1, entries 1–7). As it can be seen in Table 1, the reaction in methanol gave the desired product as a single regioisomer almost quantitatively (95 %) (Table 1, entry 9) while toluene gave the desired product in only 61 % yield (Table 1, entry 3). In general, the yields of reactions in protic solvents were higher than those in aprotic solvents. Furthermore, nearly no product was observed when H_2O was employed as a solvent (Table 1, entry 5) and it might be caused by the poor solubility of isatin and compound **3d** in water. Elevating the reaction temperature could lead to a higher reactivity (Table 1, entries 7–9). The best result was observed by refluxing the reaction mixture in methanol where **5d** was obtained in high yield (95 %) as shown in Table 1, entry 9 and the reaction time was shortened to 1.5 h. Consequently, we chose these conditions for the rest of our studies.

With the optimized reaction conditions in hand, the scope of the new multi-component reaction was investigated for compounds **3a**–**g** and different amino acids. Gratifyingly, as shown in Table 2, aryl groups with either an electron-donating or an electron-withdrawing group at the meta or para positon of the phenyl gave their corresponding products **5a**–**g**, **6a**–**g**, and **7a**–**g** in good yields ranging from 81 to 90 %. In addition, heterocyclis substituents such as thiophene also proceeded smoothly to generate the desired products **5g**, **6g**, and **7g** in good yields. It can be seen in Table 2 that the nature of the substituents in aryl groups on the 3-phenyl-1-(furan-2-yl)prop-2-enones and different amino acids had no significant effect on the reaction. The corresponding spiropyrrolidine oxindoles products **5a**–**g** and **6a**–**g** were obtained as single diastereoisomers in good yields with excellent

Table 1 Optimization of reaction conditions



3d **4** **L-Proline** **5d**

Entry	Solvent	Temp (°C)	Yield[a] (%)
1	1,4-Dioxane	60	73
2	THF	60	51
3	Toluene	60	61
4	CH_3CN	60	56
5	H_2O	60	–[b]
6	EtOH	60	86
7	CH_3OH	25	64
8	CH_3OH	40	81
9[c]	CH_3OH	Reflux	95

Unless indicated otherwise, the reaction was performed with **3d** (0.5 mmol), **4** isatin (0.5 mmol), and L-proline (0.5 mmol) in different solvents (12.0 mL) and temperatures for 3 h
[a] Isolated yield based on isatin
[b] No reaction
[c] 1.5 h

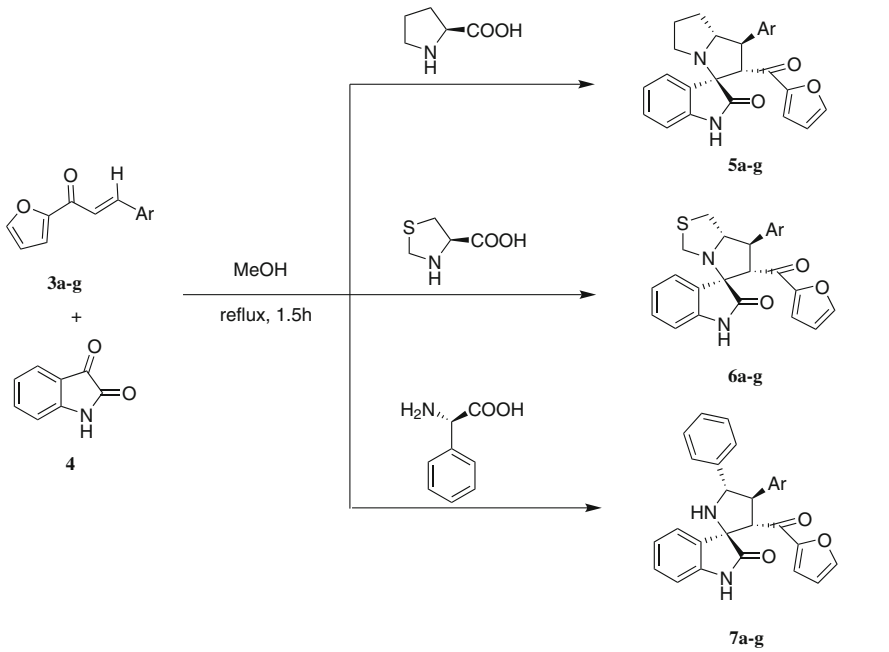
diastereoselectivities (up to > 99:1) (Table 2, entry 1–14). For compounds **7a**–**g**, the reaction took place with moderate-to-good yields ranging from 65 to 88 %, although the diastereoselectivity ratio decreased significantly (Table 2, entry 15–21).

To obtain creditable structure–activity relationships, a careful structural study was needed for the potential of regio- and diastereoisomers. The structures proposed for all products **5**–**7** were in agreement with their NMR spectra as discussed next for compound **7b**. In the ^{1}H NMR spectra of **7b**, the pyrrolidine ring proton of C-5 exhibited a doublet at δ 5.12 (J = 10.5 Hz). The proton of C-4 which was attached to the aryl appeared as a triplet at δ 4.23 (J = 10.6 Hz). The pyrrolidine ring proton of C-3 which was attached to the furan moiety exhibited a doublet at δ 4.59 (J = 10.7 Hz). The aromatic protons were distributed in the region δ 7.41–6.24. The –NH proton of the oxindole moiety appeared as a singlet at δ7.81. These chemical shift assignments confirmed the proposed structure of **7b**. Based on the calculation of the coupling constant (J-based configuration analysis, J > 10 Hz), the relative configuration of this structure should be as same as compound **7b** shown in Fig. 2 and the configuration was further confirmed by the X-ray study of a single crystal of compound **7b** (Fig. 2). The results revealed that the pyrrolidine ring adopted an envelope form with the spiro carbon being out of plane. The ^{13}C NMR of compound **7b** supported the proposed structure as well. The pyrrolidine ring carbons resonated in the region δ 68.54–54.53 ppm. The oxindole carbonyl and the carbonyl carbons resonated at δ182.32 and δ185.04, respectively (Fig. 2). The HMQC and NOESY 2D spectra data of compound **5b** were obtained. The protons of the chiral center carbons could be identified by HMQC and NOESY analysis. The proton exhibiting a doublet at δ4.58 was not related to the proton recorded as a triplet at δ3.86. This meant that the two protons are located on different sides of the ring. On the other hand, the proton at δ4.58 and the proton at δ4.22 have weak remote correlations indicating that they are located on the same side of the ring. Furthermore, the molecular weights of the desired target structures were confirmed by ESI-TOF high resolution mass spectrum (HRMS). Each spectra displayed a very prominent signal corresponding to the compound combined with one proton or one sodium cation. All analytical data is documented in the supplementary data.

A plausible mechanism for the formation of regio- and diastereoisomers could be explained as follows: the azomethine ylides, generated from the reaction of isatin and the amino acids, have two nucleophilic carbons, potentially resulting in two regioisomers. The regioselectivity observed in the formation of the product is explained on the basis that the transition state (Ts-1) leading to the observed products is likely to be more stable than the other possible one (Ts-2), which would be destabilized by interactions between the aryl ring from the styrene derivative and the amino acid chain (Fig. 3). The aryl ring attached to the pyrrolidone ring is *cis* to the carbonyl of the oxindole moiety and *trans* to the benzo group. This diastereoselectivity suggested that the transition state Ts-3 led to the minor diastereoisomers by unfavorable interactions between the phenyl ring and the benzo group of the oxindole moiety.

The 21-compound library was screened for preliminary in vitro antibacterial activity against our five ATCC-bacterial strain panel (Staphylococcus aureus ATCC 29213, Methicillin-resistant Staphylococcus aureus ATCC 43300, *E. coli* ATCC

Table 2 Scope of the reaction



Entry	Aryl	Products	Yield[a] (%)	Formula	mp (°C)	Dr[b]
1	2,4-DiClC$_6$H$_3$	**5a**	83	$C_{25}H_{20}Cl_2N_2O_3$	174–176	>99:1
2	3,4-DiClC$_6$H$_3$	**5b**	82	$C_{25}H_{20}Cl_2N_2O_3$	131–132	>99:1
3	4-OCH$_3$C$_6$H$_4$	**5c**	88	$C_{26}H_{24}N_2O_4$	162–164	>99:1
4	C$_6$H$_5$	**5d**	90	$C_{25}H_{22}N_2O_3$	185–187	>99:1
5	4-BrC$_6$H$_4$	**5e**	85	$C_{25}H_{21}BrN_2O_3$	134–135	>99:1
6	4-FC$_6$H$_4$	**5f**	86	$C_{25}H_{21}FN_2O_3$	161–162	>99:1
7	2-Thienyl	**5g**	89	$C_{23}H_{20}N_2O_3S$	185–188	>99:1
8	2,4-DiClC$_6$H$_3$	**6a**	82	$C_{24}H_{18}Cl_2N_2O_3S$	178–180	>99:1
9	3,4-DiClC$_6$H$_3$	**6b**	83	$C_{24}H_{18}Cl_2N_2O_3S$	128–130	>99:1
10	4-OCH$_3$C$_6$H$_4$	**6c**	89	$C_{25}H_{22}N_2O_4S$	161–163	>99:1
11	C$_6$H$_5$	**6d**	88	$C_{24}H_{20}N_2O_3S$	194–196	>99:1
12	4-BrC$_6$H$_4$	**6e**	81	$C_{24}H_{19}BrN_2O_3S$	133–134	>99:1
13	4-FC$_6$H$_4$	**6f**	83	$C_{24}H_{19}FN_2O_3S$	201–202	>99:1
14	2-Thienyl	**6g**	87	$C_{22}H_{18}N_2O_3S_2$	195–197	>99:1
15	2,4-DiClC$_6$H$_3$	**7a**	65	$C_{28}H_{20}Cl_2N_2O_3$	182–184	85:15
16	3,4-DiClC$_6$H$_3$	**7b**	71	$C_{28}H_{20}Cl_2N_2O_3$	220–222	85:15
17	4-OCH$_3$C$_6$H$_4$	**7c**	83	$C_{29}H_{24}N_2O_4$	181–182	98:2
18	C$_6$H$_5$	**7d**	88	$C_{28}H_{22}N_2O_3$	212–214	95:5
19	4-BrC$_6$H$_4$	**7e**	78	$C_{28}H_{21}BrN_2O_3$	221–223	89:11
20	4-FC$_6$H$_4$	**7f**	82	$C_{28}H_{21}FN_2O_3$	223–224	90:10
21	2-Thienyl	**7g**	87	$C_{26}H_{20}N_2O_3S$	203–205	96:4

The reaction was performed with **3** (1 mmol), **4** isatin (1 mmol), and amino acid (1 mmol) in methanol (12.0 mL) at reflux

[a] Isolated yield based on isatin

[b] The "Dr" referred to the diastereoselectivity and was calculated from the isolated isomers

25922, Pseudomonas aeruginos ATCC 27853 and Klebsiella pneumoniae ATCC 700603) using the standard broth dilution method [33]. As shown in Table 3, products **5**–**7**-exhibited antibacterial activities with MIC (minimum inhibitory concentration) ranging from 16 to 128 μg/mL. From the initial results, we could see that most compounds were only effective against Gram-negative bacteria, especially *P. aeruginos*. The spiro compound with pyrrolizidines scaffold, compound **5c**, showed good antibacterial activity against *P. aeruginos* at lower concentrations (16 μg/mL) and when the methoxy group was replaced by halogens (compound **5b**) there was a decrease in activity against *P. aeruginos*.

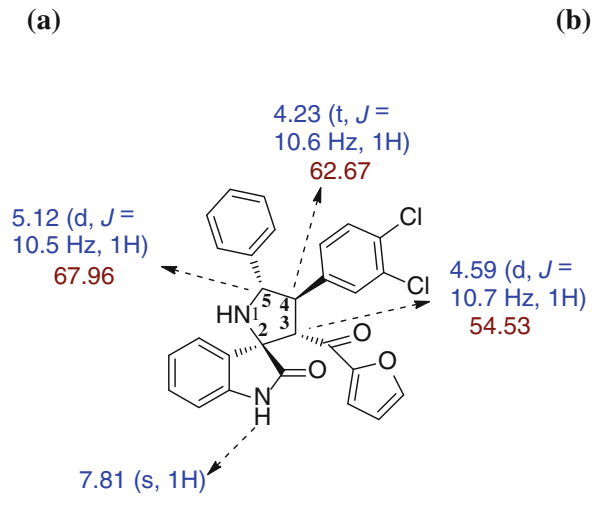


Fig. 2 **a** Selected 1^{H} and ^{13}C NMR chemical shifts of **7b.** **b** Single crystal X-ray diffraction study of compound **7b** [Crystallographic data of compound **7b** reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplement ary publication no. CCDC-897479. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk)]

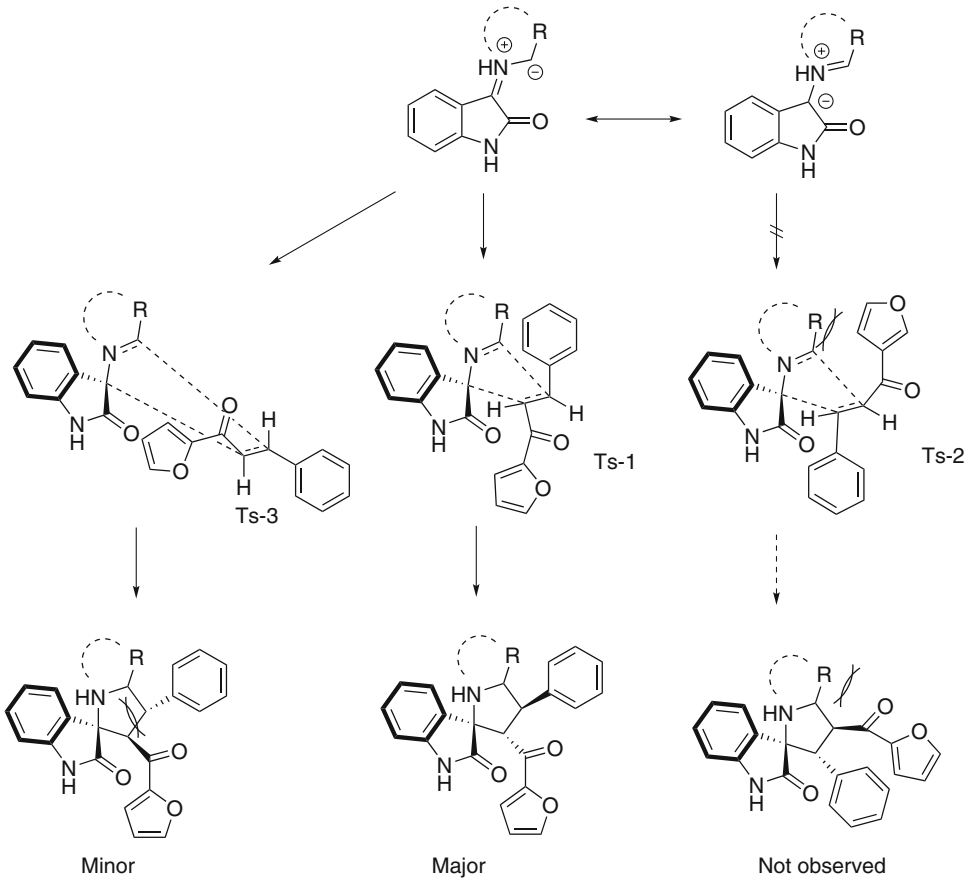


Fig. 3 Plausible mechanism for the observed regio- and diastereochemistry

For the further determination of the antibacterial spectrum of our compounds, the most promising agent **5c** was tested against many important clinical isolates. Norfloxacin, levofloxacin, and ciprofloxacin, all frequently used as antimicrobial therapeutics, were chosen as positive control. Among *P. aeruginos*, compound **5c** was active against both susceptible and multidrug-resistant isolates, with MICs of 16–32 mg/L, respectively. Though compounds **5c** showed higher MICs against the susceptible strains than the clinical used antibiotics norfloxacin, levofloxacin, and ciprofloxacin,

Table 3 Antibacterial activity of spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazoles

Compounds	MIC[a] (μg/mL)				
	Gram-positive bacteria[b]		Gram-negative bacteria[b]		
	S. aureus	MRSA	*E.coli*	*P. aeruginos*	*K. pneumoniae*
5a	64	64	128	64	128
5b	64	128	128	32	128
5c	64	128	128	16	128
5d	128	128	128	128	128
5e	128	128	128	64	128
5f	64	128	128	128	128
5g	64	128	128	64	128
6a	128	128	128	128	128
6b	128	128	128	64	128
6c	128	128	128	64	128
6d	128	64	128	128	128
6e	128	128	128	32	128
6f	128	128	128	64	128
6g	128	128	128	128	128
7a	128	128	128	128	128
7b	128	128	128	32	128
7c	128	128	128	128	128
7d	128	128	128	128	128
7e	128	128	128	32	128
7f	128	128	128	128	128
7g	128	128	128	128	128

[a] Minimum inhibitory concentrations (5×10^5 CFU/mL)
[b] Definitions of organism abbreviations: *S. aureus*, *Staphylococcus aureus* ATCC 29213; *MRSA*, Methicillin-resistant *Staphylococcus aureus* ATCC 43300; *E. coli*, *Escherichia coli* ATCC 25922; *P. aeruginos*, *Pseudomonas aeruginos* ATCC 27853; *K. pneumoniae*, *Klebsiella pneumoniae* ATCC 700603

Table 4 Anti-clinical isolates activity of compound **5c**

Organism, phenotype	MIC[a] (μg/mL)			
	5c	Norfloxacin	Levofloxacin	Ciprofloxacin
P. aeruginos ATCC 27853	16	2	1	0.25
P.aeruginos 010[b]	16	2	2	0.5
MDRP 025[c]	16	>64	>64	32
MDRP 034[d]	32	>64	>64	32

[a] Minimum inhibitory concentrations (5×10^5 CFU/mL)
[b] Quinolones-susceptible *Pseudomonas aeruginosas* No.010. Clinical isolated strain from West China Hospital, Chengdu, P. R. of China
[c] Multidrug-resistance *Pseudomonas aeruginosas* No.025. Clinical isolated strain from West China Hospital, Chengdu, P. R. of China
[d] Multidrug-resistance *Pseudomonas aeruginosas* No.034. Clinical isolated strain from West China Hospital, Chengdu, P. R. of China

the activity of compound **5c** was not affected in the screening of drug-resistant strains. This meant that compound **5c** exhibited much better activity than norfloxacin, levofloxacin and ciprofloxacin in MDRP Table 4.

Although the cellular target was not defined in the experimental antimicrobial investigations of these molecules, it was desirable to investigate the interactions between the active compounds and the enzymes, such as lanosterol demethylase, dihydrofolate reductase and topoisomerase II, which are targeted by clinically used antimicrobial drugs (Fig. 4) [34]. Docking of compound **5c** showed that the compound interacted with the active sites of the enzymes through H-bonds between its furanyl oxygen and Ser64, Ile375, Asn74, Ser128, Gly140, Lys147, Thr126 amino-acid residues, respectively. These docking results support the potential of these compounds to interfere with sterol biosyn-

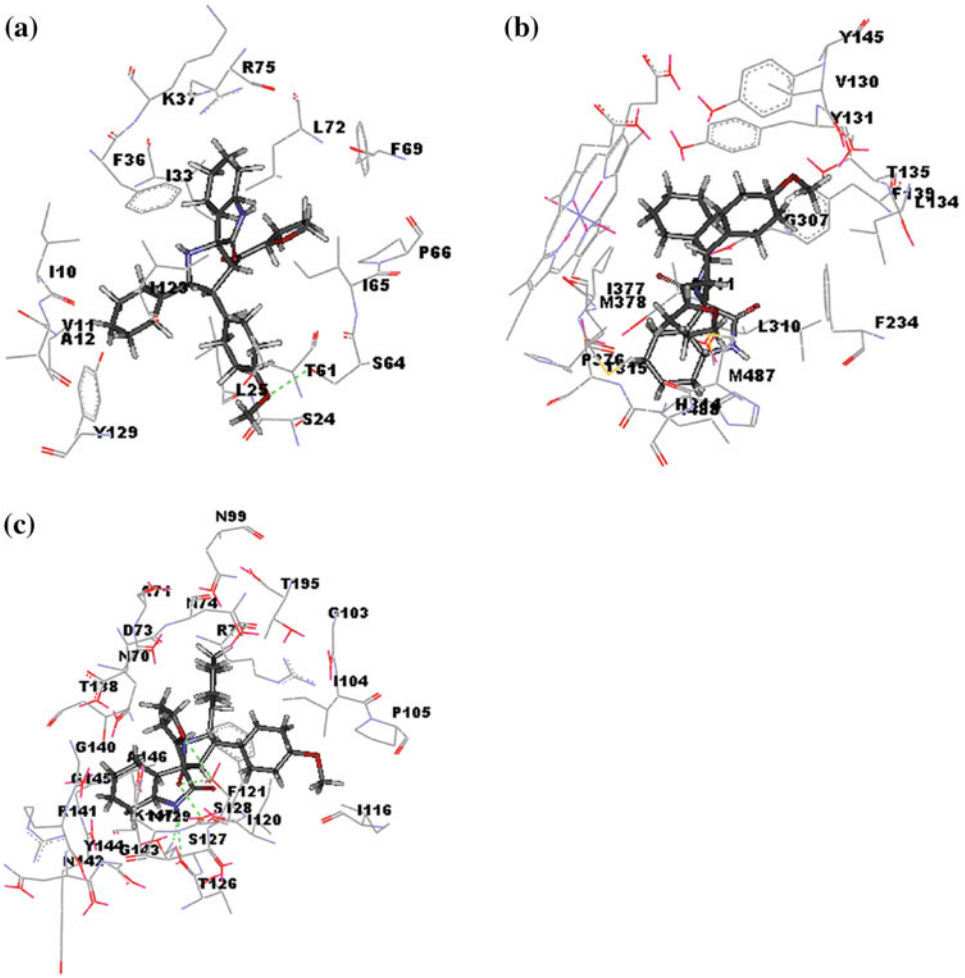


Fig. 4 Compound **5c** docked in the active site of dihydrofolate reductase (**a**), lanosterol demethylase (**b**), and topoisomerase I (**c**). H-bond distances are given in Å

thesis and DNA replication in *P. aeruginos* ultimately leading to bacterial death [35].

Conclusion

In summary, the aforementioned strategy presented a direct route to prepare biologically relevant spirooxindoles scaffolds by one-pot, multi-component 1,3-dipolar cycloaddition reaction via azomethine ylides. The advantages of this process included high bond-forming efficiency, good to high yields, simple work-up procedure, mild reaction conditions, and regio- and diastereo selectivies. The method provided rapid access to a library of spirooxindoles containing the furanyl moiety and these spiroheterocycles displayed good in vitro antibacterial activities against Gram-negative bacteria. For our study compound **5c** exhibited better activity on the multidrug resistance bacteria particularly *P. aeruginos*. The presence of the spirooxindoles, broadened the potential for further transformation of these compounds into therapeutically useful drug candidates.

Experimental

General

Thin layer chromatography (TLC) (silica gel plates GF_{254}) was used to monitor the reaction progress and the purity of the compounds: compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (20 % wt. in ethanol) followed by heating. The melting points were recorded on a SGW X-4 micro melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance III 400 MHz instrument in $CDCl_3$ using TMS as an internal standard. Chemical shifts are reported as δ values (ppm). Mass spectra were recorded on a Bruker amaZon SL spectrometer. Chemicals and solvents were either A.R. grade or purified by standard techniques.

General procedure for the synthesis of **5a–g**

A mixtrue of compound **3** (1 mmol), isatin (1 mmol), and proline (1 mmol) in methanol (12 mL) was refluxed for 1.5 h,

until completion of the reaction as indicated by TLC. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (4:1) as an eluent to afford desired product.

1′-(2,4-Dichlorophenyl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5a**)

Yellow solid, yield 83 %, mp 174–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.32 (dd, J = 12.9, 4.2 Hz, 2H), 7.27–7.11 (m, 2H), 7.06–6.94 (m, 2H), 6.73 (d, J = 7.7 Hz, 1H), 6.28 (dd, J = 3.5, 1.6 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.66–4.55 (m, 1H), 4.19–4.05 (m, 1H), 2.79 (m, 1H), 2.70–2.55 (m, 1H), 2.17–2.98 (m, 2H), 2.01–1.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.98, 180.75, 152.29, 146.72, 140.58, 135.88, 135.51, 132.95, 129.69, 129.61, 129.36, 127.61, 124.80, 122.57, 117.95, 112.32, 109.99, 73.48, 72.30, 63.89, 48.37, 47.10, 29.65, 26.75. ESI-MS (*m/z*): calcd. for 466, obsd.465 ([M-H]$^-$). HRMS (*m/z*): calcd. for 467.0929 ([M+H]$^+$), obsd.467.0937.

1′-(3,4-Dichlorophenyl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5b**)

White solid, yield 82 %, mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.60 (d, J = 1.7 Hz, 1H), 7.39–7.30 (m, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 6.99 (dd, J =8.0, 5.8 Hz, 2H), 6.72 (d, J = 7.7 Hz, 1H), 6.30 (dd, J = 3.6, 1.6 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 4.22 (m, 1H), 3.86 (t, J = 10.8 Hz, 1H), 2.76 (dd, J = 16.4, 7.9 Hz, 1H), 2.68–2.56 (m, 1H), 2.04–1.88 (m, 2H), 1.88–1.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.04, 180.60, 152.19, 146.94, 140.51, 140.02, 132.67, 131.05, 130.65, 130.25, 129.65, 127.50, 127.56, 124.72, 122.45, 118.28, 112.33, 109.99, 73.42, 71.40, 64.46, 51.46, 48.31, 29.98, 26.83. ESI-MS (*m/z*): calcd. for 466.09, obsd.465([M-H]$^-$). HRMS (*m/z*): calcd. for 467.0929 ([M+H]$^+$), obsd.467.0927.

1′-(4-Methoxyphenyl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5c**)

White solid, yield 88 %, mp 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.31 (dd, J = 11.0, 4.2 Hz, 2H), 7.15 (t, J = 7.7 Hz, 1H), 7.00 (dd, J = 13.2, 5.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 7.7 Hz, 1H), 6.26 (dd, J = 3.6, 1.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.22 (dt, J = 10.0, 6.1 Hz, 1H), 3.99–3.82 (m, 1H), 3.76 (s, 3H), 2.73 (dd, J = 12.1, 4.4 Hz, 1H), 2.67–2.55 (m, 1H), 2.07–1.88 (m, 2H), 1.7–1.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.26, 181.08, 158.60, 152.39, 146.78, 140.51, 131.42, 129.46, 129.10, 127.72, 125.08, 122.37, 118.18, 114.10, 112.15, 110.01, 73.77, 71.72, 64.47, 55.23, 51.67, 48.33, 30.30, 27.07. ESI-MS(*m/z*): calcd. for 428, obsd.427([M-H]$^-$). HRMS (*m/z*): calcd. for 429.1814 ([M+H]$^+$), obsd.429.1820.

1′-Phenyl-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5d**)

White solid, yield 90 %, mp 185–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.46–7.38 (m, 2H), 7.24 (dd, J = 10.4, 4.9 Hz, 4H), 7.18–7.04 (m, 2H), 7.00–6.88 (m, 2H), 6.68 (d, J = 7.7 Hz, 1H), 6.24–6.16 (m, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.26 – 4.13 (m, 1H), 3.86 (dd, J = 11.3, 10.2 Hz, 1H), 2.76–2.62 (m, 1H), 2.62–2.50 (m, 1H), 2.15–1.78 (m, 3H), 1.78–1.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.16, 180.18, 151.32, 145.75, 139.56, 138.49, 128.46, 127.65, 127.13, 126.67, 125.97, 124.01, 121.35, 117.12, 111.14, 109.05, 72.79, 70.81, 63.33, 51.33, 47.31, 29.29, 26.03. ESI-MS(*m/z*): calcd. for 398, obsd.397([M-H]$^-$). HRMS (*m/z*): calcd. for 399.1709 ([M+H]$^+$), obsd.399.1737.

1′-(4-Bromophenyl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5e**)

White solid, yield 85 %, mp 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.48–7.31 (m, 6H), 7.15 (t, J = 7.7 Hz, 1H), 6.99 (dd, J = 13.5, 5.6 Hz, 2H), 6.73 (d, J = 7.7 Hz, 1H), 6.28 (dd, J = 3.6, 1.6 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.26–4.16 (m, 1H), 3.94–3.83 (m, 1H), 2.75 (dd, J = 11.9, 4.6 Hz, 1H), 2.69–2.55 (m, 1H), 2.07–1.85 (m,3H), 1.84–1.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.09, 180.86, 152.26, 146.90, 140.52, 138.60, 131.81, 129.92, 129.59, 127.63, 124.86, 122.43, 120.89, 118.23, 112.27, 110.04, 73.61, 71.55, 64.43, 51.81, 48.33, 30.13, 26.95. ESI-MS(*m/z*): calcd. for 476, obsd.395([M-H]$^-$). HRMS (*m/z*): calcd. for 477.0814 ([M+H]$^+$), obsd.477.0809.

1′-(4-Fluorophenyl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5f**)

White solid, yield 86 %, mp 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.45 (dd, J = 8.5, 5.4 Hz, 2H), 7.34–7.25(m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.06–6.89 (m, 4H), 6.73 (d, J = 7.7 Hz, 1H), 6.27 (dd, J = 3.5, 1.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.26–4.13 (m, 1H), 3.97–3.82 (m, 1H), 2.83–2.66 (m, 1H), 2.66–2.51 (m, 1H),

2.06–1.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.18, 181.00, 160.70, 152.31, 146.87, 140.54, 135.17, 129.62, 127.64, 124.93, 122.42, 118.21, 115.65, 115.44, 112.24, 110.05, 73.65, 71.69, 64.55, 51.61, 48.33, 30.19, 26.99. ESI-MS(*m/z*): calcd. for 416, obsd.415([M-H]$^-$). HRMS (*m/z*): calcd. for 417.1614([M+H]$^+$), obsd.417.1617.

1′-(Thiophen-2-yl)-2′-(furan-2-carbonyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (**5g**)

White solid, yield 89 %, mp 185–188 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.36 (d, J = 1.0 Hz, 1H), 7.27 (m, 1H), 7.20–7.11 (m, 2H), 7.06–6.97 (m, 3H), 6.92 (dd, J = 5.1, 3.5 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.29 (dd, J = 3.6, 1.7 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.26 (m, 2H), 2.77–2.56 (m, 2H), 2.09 – 1.90 (m, 2H), 1.90–1.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.79, 180.96, 152.22, 147.05, 142.53, 140.54, 129.61, 127.65, 126.96, 125.00, 124.74, 123.84, 122.42, 118.57, 112.26, 110.21, 73.88, 71.74, 64.93, 48.28, 47.37, 30.42, 27.12. ESI-MS(*m/z*): calcd. for 404, obsd.405([M+H]$^+$). HRMS (*m/z*): calcd. for 427.1092 ([M+Na]$^+$), obsd.427.1094.

General procedure for the synthesis of **6a**–**g**

A mixtrue of compound **3** (1 mmol), isatin (1 mmol) and thiaproline (1 mmol) in methanol (12 mL) was refluxed for 1.5 h, until completion of the reaction as indicated by TLC. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (4:1) as an eluent to afford desired product.

7′-(2,4-Dichlorophenyl)-6′-(furan-2-carbonyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6a**)

White solid, yield 82 %, mp 178–180 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 33.4 Hz, 1H), 7.55–7.45 (m, 1H), 7.33 (dd, J = 24.7, 5.7 Hz, 1H), 7.18–7.06 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 3.5 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 6.45 (dd, J = 3.5, 1.5 Hz, 1H), 6.25 (d, J = 2.2 Hz, 1H), 4.60 (m, 2H), 4.21 (s, 1H), 3.83 (d, J = 10.4 Hz, 1H), 3.66 (d, J = 6.8 Hz, 1H), 3.08 (s, 1H), 3.06–2.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 168.609,150.93, 148.95, 145.77, 139.30, 132.52, 129.18, 128.93, 128.57, 127.72, 126.68, 121.80, 121.62, 117.07, 116.49, 111.43, 108.47, 73.87, 73.03, 60.75, 53.35, 44.57, 35.01. ESI-MS(*m/z*): calcd. for 484.04, obsd.483([M-H]$^-$). HRMS (*m/z*): calcd. for 507.0313 ([M+Na]$^+$), obsd.507.0313.

7′-(3,4-Dichlorophenyl)-6′-(furan-2-carbonyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6b**)

White solid, yield 83 %, mp 128–130 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.59 (dd, J = 23.7, 4.6 Hz, 2H), 7.48–7.31 (m, 3H), 7.18 (t, J = 7.7 Hz, 1H), 7.10–6.92 (m, 2H), 6.69 (d, J = 7.7 Hz, 1H), 6.32 (dd, J = 3.5, 1.6 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.42–4.25 (m, 1H), 4.01–3.84 (m, 2H), 3.52 (d, J = 10.3 Hz, 1H), 3.07 (dd, J = 11.7, 6.3 Hz, 1H), 2.97 (dd, J = 11.7, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.82, 179.83, 151.90, 146.97, 140.24, 139.08, 132.93, 131.62, 130.84, 130.30, 128.64, 127.81, 122.77, 118.38, 112.45, 109.75, 74.27, 62.66, 58.50, 54.26, 49.92, 36.25, 18.46. ESI-MS(*m/z*): calcd. for 484.04, obsd.483([M-H]$^-$). HRMS (*m/z*): calcd. for 507.0313 ([M+Na]$^+$), obsd.507.0313.

6′-(Furan-2-carbonyl)-7′-(4-methoxyphenyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6c**)

Yellow solid, yield 89 %, mp 161–163 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 0.8 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 3.5 Hz, 1H), 6.79 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 7.7 Hz, 1H), 6.21 (dd, J = 3.5, 1.5 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.36–4.20 (m, 1H), 3.84 (dt, J = 9.9, 5.6 Hz, 2H), 3.68(s,3H), 3.45 (d, J = 10.4 Hz, 1H), 2.96 (qd, J = 11.7, 4.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.15, 179.25, 157.89, 151.13, 145.77, 139.22, 129.47, 128.98, 128.31, 127.86, 122.07, 121.61, 117.19, 113.25, 111.22, 108.67, 73.69, 73.45, 61.52, 57.46, 54.23, 53.58, 49.34, 35.43, 17.42. ESI-MS(*m/z*): calcd. for 446.13, obsd.445([M-H]$^-$). HRMS (*m/z*): calcd. for 469.1198 ([M+Na]$^+$), obsd.469.1205.

6′-(Furan-2-carbonyl)-7′-phenyl-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6d**)

White solid, yield 88 %, mp 194–196 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.3 Hz, 2H), 7.34 (dd, J = 10.5, 4.4 Hz, 3H), 7.29–7.13 (m, 1H), 7.04 (td, J = 7.6, 0.8 Hz, 1H), 6.96 (d, J = 3.5 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.28 (dd, J = 3.6, 1.6 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.44–4.32 (m, 1H), 4.02–3.86 (m, 2H), 3.53 (d, J = 10.4 Hz, 1H), 3.12–2.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.10, 180.34, 152.12, 146.80, 140.30, 138.66, 130.06, 128.89, 128.37, 127.48, 123.09, 122.68, 118.19, 112.27, 109.76, 74.81, 74.50, 62.53, 54.50, 51.02, 36.47. ESI-MS(*m/z*): calcd. for 416.12, obsd.415 ([M-H]$^-$). HRMS (*m/z*): calcd. for 439.1092 ([M+Na]$^+$), obsd.439.1113.

7′-(4-Bromophenyl)-6′-(furan-2-carbonyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6e**)

White solid, yield 81 %, mp 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.47–7.24 (m, 4H), 7.10 (t, J = 7.3 Hz, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 3.5 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 6.23 (dd, J = 3.5, 1.6 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.38–4.17 (m, 1H), 3.95–3.76 (m, 2H), 3.45 (d, J = 10.3 Hz, 1H), 2.95 (ddd, J = 13.7, 11.7, 4.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.93, 178.96, 151.00, 145.86, 139.23, 136.73, 130.99, 129.10, 129.07, 127.71, 121.94, 121.69, 120.39, 117.23, 111.33, 108.69, 73.42, 73.22, 61.64, 57.46, 53.27, 49.33, 35.28, 17.43. ESI-MS(*m/z*): calcd. for 494.03, obsd.495([M-H]$^-$). HRMS (*m/z*): calcd. for 517.0197 ([M+Na]$^+$), obsd.517.0199.

7′-(4-Fluorophenyl)-6′-(furan-2-carbonyl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6f**)

White solid, yield 83 %, mp 201–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.55–7.39 (m, 2H), 7.36 (d, J = 1.0 Hz, 1H), 7.18 (td, J = 7.7, 1.2 Hz, 1H), 7.08–6.92 (m, 4H), 6.70 (d, J = 7.7 Hz, 1H), 6.30 (dd, J = 3.6, 1.7 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.40–4.29 (m, 1H), 4.00–3.86 (m, 2H), 3.53 (d, J = 10.3 Hz, 1H), 3.03 (ddd, J = 13.9, 11.7, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.05, 180.13, 152.07, 146.87, 140.26, 134.34, 130.11, 129.92, 129.84, 128.77, 123.00, 122.71, 118.23, 115.89, 112.33, 109.74, 74.64, 74.30, 62.73, 58.49, 54.39, 50.20, 36.34, 18.45. ESI-MS(*m/z*): calcd. for 434.11, obsd.435([M+H]$^+$). HRMS (*m/z*): calcd. for 457.0998 ([M+Na]$^+$), obsd.457.0997.

6′-(Furan-2-carbonyl)-7′-(thiophen-2-yl)-3′,6′,7′,7a′-tetrahydro-1′H-spiro[indoline-3,5′-pyrrolo[1,2-c]thiazol]-2-one (**6g**)

White solid, yield 87 %, mp 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 1.0 Hz, 1H), 7.23–7.13 (m, 2H), 7.05 (ddd, J = 13.1, 11.4, 3.4 Hz, 3H), 6.94 (dd, J = 5.1, 3.5 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 6.32 (dd, J = 3.6, 1.6 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.47 – 4.35 (m, 1H), 4.27 (dd, J = 11.7, 9.9 Hz, 1H), 3.90 (d, J = 10.6 Hz, 1H), 3.52 (d, J = 10.6 Hz, 1H), 3.21–3.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.75, 179.93, 152.03, 147.07, 141.46, 140.20, 130.16, 128.93, 127.15, 125.77, 124.31, 122.81, 122.70, 118.62, 112.34, 109.80, 74.73, 74.66, 62.89, 54.72, 46.12, 36.54, 18.46. ESI-MS(*m/z*): calcd. for 422.07, obsd.421([M-H]$^-$). HRMS (*m/z*): calcd. for 445.0657 ([M+Na]$^+$), obsd.445.0660.

General procedure for the synthesis of **7a–g**

A mixtrue of compound **3** (1 mmol), isatin (1 mmol) and phenylglycine (1 mmol) in methanol (12 mL) was refluxed for 1.5 h, until completion of the reaction as indicated by TLC. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography using petroleum ether/ethyl acetate (4:1) as an eluent to afford desired product.

4′-(2,4-Dichlorophenyl)-3′-(furan-2-carbonyl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7a**)

Yellow solid, yield 65 %, mp 182–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.73 (m, 2H), 7.37 –6.86 (m, 13H), 6.69 (d, J =7.8 Hz, 1H), 6.26 (t, J =1.6 Hz, 1H), 5.20 (d, J =10.4 Hz,1H), 4.88 (t, J = 28 Hz, 1H), 4.59 (d, J =10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.75, 182.09, 152.60, 146.29, 140.03, 139.17, 135.82, 135.42, 132.99, 130.18, 129.55, 129.40, 128.84, 128.39, 128.01, 127.49, 127.08, 126.13, 123.27, 116.89, 112.46, 109.34, 68.61, 62.22, 49.61. ESI-MS(*m/z*): calcd. for 502.09, obsd.525([M+Na]$^+$). HRMS (*m/z*): calcd. for 525.0749 ([M+Na]$^+$), obsd.525.0755.

4′-(3,4-Dichlorophenyl)-3′-(furan-2-carbonyl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7b**)

Yellow solid, yield 71 %, mp 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.46–7.20 (m, 5H), 7.07– 7.16 (m, 5H), 6.99 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 3.5 Hz, 1H), 6.66 (d, J = 8 Hz, 2H), 6.25 (d, J = 1.9 Hz, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.59 (d, J = 10.7 Hz, 1H), 4.23 (t, J = 10.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.04, 182.33, 152.72, 146.34, 140.24, 140.01, 138.85, 129.45, 129.25, 128.55, 128.32, 127.71, 127.15, 127.07, 126.16, 123.22, 116.93, 112.30, 109.32, 68.54, 67.96, 62.67, 54.54. ESI-MS(*m/z*): calcd. for 502.09, obsd.503([M+H]$^+$). HRMS (*m/z*): calcd. for 525.0749 ([M+Na]$^+$), obsd.525.0748.

3′-(Furan-2-carbonyl)-4′-(4-methoxyphenyl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7c**)

Yellow solid, yield 83 %, mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.42–6.99 (m, 9H), 7.00 (d, J = 7.5 Hz, 1H), 7.04–6.82 (m, 3H), 6.78 (d, J = 8.3 Hz, 2H), 6.62 (dd, J = 27.7, 8.0 Hz, 1H), 6.28–6.21 (m, 1H), 5.06 (d, J = 10.5 Hz, 1H), 4.53 (t, J = 11.8 Hz, 1H), 4.17 (t, J = 10.6 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.14, 182.48, 158.51, 152.75, 146.35, 140.38, 140.01, 130.76, 129.58, 129.48, 129.22, 128.30, 127.66, 127.16, 126.15, 123.21, 116.94, 113.94, 112.29, 109.36, 68.50, 67.90, 62.71, 55.15, 53.87. ESI-MS(*m/z*): calcd.

for 464.17, obsd.465([M+H]$^+$). HRMS (*m/z*): calcd. for 487.1634 ([M+Na]$^+$), obsd.487.1630.

3′-(Furan-2-carbonyl)-4′,5′-diphenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7d**)

Yellow solid, yield 88 %, mp 212–214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.52 (m, 2H), 7.45–7.29 (m, 6H), 7.29 – 7.05 (m, 6H), 7.05–6.84 (m, 2H), 6.68 (d, J = 7.7 Hz, 1H), 6.27 (d, J = 3.4 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.48 (d, J = 10.5 Hz, 1H), 4.17 (t, J = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.71, 182.29, 152.51, 146.51, 140.07, 139.56, 139.45, 132.53, 131.08, 130.53, 130.37, 129.43, 129.01, 128.53, 128.12, 128.07, 127.09, 126.00, 123.27, 117.13, 112.49, 109.48, 68.42, 67.65, 62.45, 53.62. ESI-MS(*m/z*): calcd. for 434.16, obsd.435([M+H]$^+$). HRMS (*m/z*): calcd. for 457.1528 ([M+Na]$^+$), obsd.457.1537.

4′-(4-Bromophenyl)-3′-(furan-2-carbonyl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7e**)

Yellow solid, yield 78 %, mp 221–223 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.45–6.94 (m, 14H), 6.85 (d, J = 3.6 Hz, 1H), 6.67 (d, J = 7.7 Hz, 1H), 6.28–6.22 (m, 1H), 5.08 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 10.7 Hz, 1H), 4.19 (t, J = 10.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.86, 182.36, 152.59, 146.48, 140.09, 139.79, 137.97, 131.70, 130.29, 129.37, 129.17, 128.44, 127.93, 127.12, 126.06, 123.25, 120.95, 117.06, 112.43, 109.48, 68.47, 67.77, 62.51, 53.98. ESI-MS(*m/z*): calcd. for 512.07, obsd.513 ([M+H]$^+$). calcd. for 535.0633 ([M+Na]$^+$), obsd.535.0638.

4′-(4-Fluorophenyl)-3′-(furan-2-carbonyl)-5′-phenylspiro[indoline-3,2′-pyrrolidin]-2-one (**7f**)

Yellow solid, yield 82 %, mp 222–224 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.45–7.28 (m, 5H), 7.25 (d, J = 7.0 Hz, 4H), 7.08 (t, J = 7.7 Hz, 1H), 6.93 (ddd, J = 30.8, 18.7, 5.5 Hz, 4H), 6.73 (d, J = 9.5 Hz, 1H), 6.66 (d, J = 7.7 Hz, 1H), 6.30–6.23 (m, 1H), 5.07 (d, J = 10.5 Hz, 1H), 4.52 (d, J = 10.7 Hz, 1H), 4.20 (t, J = 10.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.97, 182.26, 152.67, 146.41, 139.99, 134.55, 130.04, 129.96, 129.32, 128.38, 127.84, 127.11, 126.13, 123.25, 116.99, 115.53, 115.32, 112.37, 109.35, 68.39, 67.94, 62.60, 53.81. ESI-MS(*m/z*): calcd. for 452.15, obsd.453([M+H]$^+$). HRMS (*m/z*): calcd. for 475.1434 ([M+Na]$^+$), obsd.475.1433.

3′-(Furan-2-carbonyl)-5′-phenyl-4′-(thiophen-2-yl)spiro[indoline-3,2′-pyrrolidin]-2-one (**7g**)

Yellow solid, yield 87 %, mp 203–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.50 (m, 2H), 7.29–7.33(m, 6H), 7.09 (dd, J = 10.2, 6.2 Hz, 2H), 7.03–6.80 (m, 4H), 6.67 (d, J = 7.6 Hz, 1H), 6.31–6.24 (m, 1H), 5.14–4.99 (m, 1H), 4.57 (d, J = 4.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.64, 182.12, 152.57, 146.65, 141.74, 140.07, 139.80, 129.38, 129.31, 128.45, 128.04, 127.45, 126.85, 126.12, 125.70, 124.01, 123.26, 117.36, 112.41, 109.54, 68.52, 62.35, 63.13, 49.61. ESI-MS(*m/z*): calcd. for 440.12, obsd.441([M+H]$^+$). HRMS (*m/z*): calcd. for 463.1092 ([M+Na]$^+$), obsd.463.1095.

In vitro minimum inhibitory concentration assay

MICs were determined by a microdilution method with MuellereHinton Broth (MHB) for staphylococci and Lennox Broth (LB) for Enterococci, following the National Committee for Clinical Laboratory Standards (NCCLS) (now called the Clinical Laboratory Standards Institute [CLSI]). The stock solutions of test compounds were diluted to give a serial 2-fold series, with final chemical concentrations ranging from 64 to 0.0125 μg/mL. The MIC was defined as the lowest concentration of the chemical that inhibited the development of visible bacterial growth after an incubation for 16 h at 37 °C. The MICs of standard antibiotics (norfloxacin, levofloxacin and ciprofloxacin) were determined by the same method.

Molecular docking procedure

Compounds were built using the builder toolkit of the software package Discover Studio 3.1 [36]. The crystal coordinates of lanosterol demethylase (pdb ID: 3JUS), dihydrofolate reductase (pdb ID: 3NZ6) and topoisomerase II (pdb ID: 1QZR) were downloaded from protein data bank, carrying econazole, 6-{3-[(2,4-diamino-5-methylpyrido[2,3-d]pyrimidin-6-yl)methyl]-4- methoxyphenoxy} hexanoic acid (a trimethoprim analogue) and dextrazoxazone as co-crystallized ligands, respectively. Structure of compound **5c** was pasted in the workspace carrying structures of the enzymes. The docking program implements an efficient grid based docking algorithm which approximates an exhaustive search within the free volume of the binding site cavity. The conformational space was explored by the geometry optimization of the flexible ligand (rings were treated as rigid) in combination with the incremental construction of the ligand torsions. Thus, docking occurs between the flexible ligand parts of the compound and enzyme. The ligand orientation was determined by a scoring function based on Ligscore and the final positions were ranked by lowest interaction energy values. H-bond and hydrophobic interactions between the compound and enzyme were explored.

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