HHS Public Access

Author manuscript

Bioorg Med Chem Lett. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Bioorg Med Chem Lett. 2015 October 1; 25(19): 4225–4231. doi:10.1016/j.bmcl.2015.07.105.

2-(3′-Indolyl)-*N*-arylthiazole-4-carboxamides: Synthesis and evaluation of antibacterial and anticancer activities

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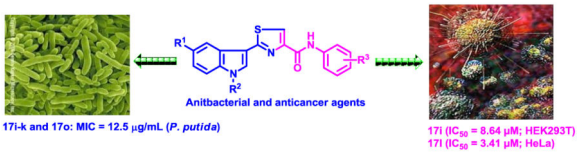
Abstract

A new series of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** has been designed and synthesized. Initial reaction of readily available thioamides **15** with bromopyruvic acid under refluxing conditions produced different thiazole carboxylic acids **16** which upon coupling with arylamines by using EDCI.HCl and HOBt afforded diverse arylthiazole-4-carboxamides **17a-p** in 78-87% yields. Antibacterial activity evaluation against Gram-positive and Gram-negative bacterial strains led to compounds **17i-k** and **17o** as potent and selectively (Gram-negative) antibacterial agents. The cytotoxicity of thiazole carboxamides **17a-p** was also evaluated on a panel of human cancer cell lines. Among the tested derivatives, compounds **17i** (IC_{50} = 8.64 μM; HEK293T) and **17l** (IC_{50} = 3.41 μM; HeLa) were identified as the most potent analogues of the series. Preliminary mechanism of action studies of thiazole carboxamide **17i** suggested that its cytotoxicity against HeLa cells involves the induction of cell death by apoptosis.

Graphical Abstract



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Supplementary Material

Supplementary data (experimental procedures and characterization data for compounds (**17a–p**) associated with this article can be found, in the online version, at http://dx.doi.org/

Keywords

Indoles; Thiazole carboxamides; Antibacterial; Cancer; Cytotoxicity; Apoptosis

Indole derivatives are recognized as a class of important heterocycles for their useful pharmacological properties.[1] Existing studies have proved their wide range of biological activities such as antiviral, antimicrobial and antitumor agents. Indole ring system is found in a number of clinically useful therapeutic agents such as, indomethacin, indoramin, and indorenate.[2] Moreover, several indole containing molecules have been documented for their interesting antibacterial and anticancer activities. For example, 3-thiazol-2′-ylindole (Camalexin) **1** is the characteristic phytoalexin of *Arabidopsis thaliana*, which is induced by a variety of plant pathogens as well as human tumor cell lines.[3] Isolated from marine sponges, the bis(indole)alkaloids Topsentins[4] (**2**) and Nortopsentins[5] (structure not shown) have received increasing attention due to their interesting anticancer properties. In 2012, Li *et al*. explored 2-indolyl-4-benzoylimidazole (**3**) as a tubulin targeting anticancer agent with an average IC_{50} value of 3.8 nM against the tested cancer cell lines (Fig. 1).[6] Ki-Bong Oh group explored the antibacterial activity of bis(indole) class of alkaloids including topsentins and hamacanthins (**4**), which exhibited significant antibacterial activity against Gram-positive and Gram-negative bacteria in addition to anticancer activity.[7] Hoemann et al has prepared a combinatorial library of 2-(1*H*-indol-3-yl)quinolines (**5**) which were effective against methicillin-resistant Staphylococcus aureus with an MIC < 1.0 μg/mL.[8] More recently, Singh et al. synthesized bis(indole)glyoxamide (**6**) and evaluated as potent antibacterial candidates.[9]

Similarly, over the past few years, various substituted thiazole analogues have been reported to demonstrate diverse biological activities including antimicrobial, antimalarial, antitubercular, antiviral and anticancer activities.[10,11,12] Thiazole nucleus is also an essential part of all the available penicillins.[13] Among the thiazoles, substituted thiazolecarboxamides exhibited encouraging antibacterial and anticancer activities.[14] For examples; thiazolecarboxamide scaffold bearing analogues of Distamycin (**7**) were reported by Suckling et al. as an antibacterial agent. Very recently, Rostom and co-worker synthesized 2-amino-4-methylthiazole-5-carboxylates (**8**) and evaluated for their preliminary *in vitro* antimicrobial and anticancer activities. Most of synthesized analogues were found to be active against various bacterial strains and malignant cells.[15] Hofle and co-workers isolated peptides namely Tubulysins A and D (**9**) from the myxobacteria *Archangium gephyra* and *Angiococcus disciformis*, respectively,[16,17] were found to display a broad range of anticancer activity.[18] In 2012, Huang and co-worker identified 2-aryl-*N*-(2-(piperazin-1-yl)phenyl)-thiazole-4-carboxamide (ALIS hit **10**), as a potent CHK1 inhibitor.[19] Various 2-phenylthiazole-4-carboxamides **11** (IC_{50} = 2-10 μM) and **12** (IC_{50} = 10-25 μM) synthesized by Foroumadi *et al*. were found to be potent anticancer agents against a panel of human cancerous cells.[20, 21]

In the light of above mentioned observations regarding potential of indole-based antibacterial and anticancer agents, thiazole carboxamides and in pursuit of previous results on indole derivatives, [22] we designed a new library of 2-(3′-indolyl)-*N*-arylthiazole-4-

carboxamides **17a-p** by incorporating crucial structural features of both the bioactive scaffolds (Fig. 3). The goal was to develop potential small molecules that display either antibacterial or anticancer properties, or react with both species. Such molecules provide a unique opportunity to uncover drug mechanism across divergent species. More importantly, the resulting SAR studies could be further used to design specific anti-bacterial agents that do not cross-react with mammalian targets and vice versa. Such kind of specificity is extremely desirable for developing anti-infective agents which do not target human tissues, and thus likely to exhibit minimal collateral toxicity.

The 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** were prepared according to Scheme 1. Precursor thioamides **15** were prepared from the corresponding indole by known methods.[23,24] Reaction of thioamide **15** with bromopyruvic acid under refluxing conditions led to thiazole carboxylic acids **16** in good yields. Diverse carboxylic acids **16** were coupled with various arylamines in the presence of coupling reagent, EDCI.HCl and HOBt to prepare arylthiazole-4-carboxamides **17a-p** in 78-87% yields.[25] Structures of thiazole-carboxamides **17a-p** were elucidated through their IR, NMR (^{1}H &^{13}C) and Mass spectral analysis. In IR spectra, a characteristic sharp peak at ~1660 cm^{-1} was observed due to C=O stretching of an amide functional group. Carbon of an amide moiety (CONH) was resonated at ~163 ppm in the ^{13}C NMR spectra of compounds **17a-p**.

Initially, we screened all the synthesized compounds for their *in vitro* antibacterial activity against two Gram-positive bacteria Staphylococcus aureus (MTCC 96), *Bacillus* subtilis (MTCC 121) and two Gram-negative bacteria *Escherichia coli* (MTCC 1652), *Pseudomonas putida* (MTCC 102) bacterial strains. Ciprofloxacin was used as a standard drug and the resulting activity (zone of inhibition (ZOI) and minimum inhibitory concentration (MIC)) are given in Table 1.

Antibacterial activity results (Table 1) demonstrated that the analogue **17i** possessing 5-methoxyindole and trimethoxyphenyl substituents displayed excellent activity against Gram-negative bacteria (ZOI = 18 mm and MIC = 12.5 μg/mL); comparable to standard drug Ciprofloxacin but almost inactive against Gram-positive bacteria. Interestingly, replacement of a C-5 methoxy group on indole ring with bromine in compound **17i** led to **17k** endowed with good antibacterial activity against tested bacterial strains (ZOI = 14-16 mm; MIC = 12.5-50 μg/mL). Methoxyphenyl analogue **17j** also exhibited high antibacterial activity with MIC value of 12.5 μg/mL in *P. putida* strain. Further, we also observed that the protection of indole *N*-H as 4-chlorobenzyl group was beneficial for the activity (**17a** *vs* **17n** and **17c** *vs* **17o**), especially **17o** had MIC values (12.5 μg/mL) similar to Ciprofloxacin. Remaining compounds (**17a-h**, **17l-n** and **17p**) of the series displayed moderate activity against the tested bacterial strains. Among the synthesized compounds, **17i-j** and **17o** were found to be most potent and selective against Gram-negative bacteria. Compound **17k** was also found to be equally effective against Gram-negative bacteria (MIC = 12.5 μg/mL; *P. putida*) in addition to moderate activity against *B. cereus* strain. Results from antibacterial activity study shows that substitution on indole (5-OMe/Br), methoxyphenyl substitution on arylamino part and protection of indole *N*-H with 4-chlorobenzyl moiety, were beneficial for their antibacterial activity.

Once we identified the most potent antibacterial agents, compounds **17i** and **17j** were selected to evaluate their time-dependent killing effect against tested bacterial strains *E. coli* (MTCC 1652) and *P. putida* (MTCC 102). Compounds **17i** and **17j** with higher than MIC were incubated with log phase culture of *E. coli* and *P. putida* at 37 °C and change in optical density (OD_{600}) was monitored at different time intervals (Fig. 4). The results showed a significant reduction in number of bacterial cells after addition of **17i** and **17j** at 4×MIC. Against *E. coli* compound **17i** was found to be more effective as compared to **17j** even up to 6 h. Similarly against *P.putida*, compound **17j** was found to be less effective as compared to **17i**, however, both the compounds inhibited bacterial growth from 2-3 h and arrested till 6 h. At 4×MIC compound **17i** exhibited the potent inhibition of growth as compared to **17j**. Thus the present study results illustrated that **17i** and **17j** were capable of inhibiting the bacterial growth within few hours of initial interactions.

After determining the antibacterial activities of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p**, we next evaluated their potential anticancer activities in human embryonic kidney 293 cells (HEK 293T), human prostate (PC3, LNCaP and castration-resistant prostate cancer cell line C4-2), cervical (HeLa), and breast (MDA-MB-231) cancer cell lines using MTT assay. Doxorubicin was used as a reference drug. We initially analyzed potential cytotoxicity of these compounds in aforementioned cancer cell lines in the presence of FBS (Table 1).

The cells growing in 10% FBS were treated with varying concentrations of (3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** for 48 h and cytotoxicity evaluated using MTT assay. The cytotoxicity results of compounds **17a-p** are expressed as IC_{50} values in micromolar (Table 2).

Surprisingly, most of the compounds showed minimal cytotoxic effect following 48 h exposure of the micromolar concentrations of the compounds. A few exceptions, including compound **17i** (Table 2) was highly potent and selective for HEK293T and HeLa cells. Compound **17k**, which contains a bromo group instead of methoxy at R^1 position compared to **17i**, selectively inhibited HEK293T cells, but had negligible effect on HeLa cells.

These results suggested that either most of these (3′-indolyl)-*N*-arylthiazole-4-carboxamides are ineffective as anti-cancer agents or they are not readily available to cells. The latter concern was also prompted by the fact that compounds **17c-g** and **17j** in this series displayed poor water solubility and were precipitated out of solution when added to cells in an overall DMSO concentration of 0.05-0.1% (Table 2). Similar to fatty acids, several water-insoluble compounds are known to avidly bind serum proteins, which drastically reduces the effective concentration of free molecules to enter the cells.[26] Further, serum in growth media can also interfere with MTT reagent leading to overestimation of cell growth and an underestimation of potential cytotoxicity of compounds.[27,28] As a result, these compounds are rendered ineffective in the presence of serum, although when serum is removed, they promote significant cell death.

Therefore, we examined the potential cytotoxicity of these compounds in cells in the absence of serum. The cells were freshly plated and grown in serum containing media. After

12h, the media was replaced with serum free media and varying concentrations of the compounds were added. After 48h, cell viability was analyzed using MTT assay. As expected, we observed ~10-20% cell growth with no cell death in DMSO-treated cells after 48 h of treatment, thereby ruling out any artifact that can potentially interfere with cytotoxicity assays. Importantly, in the absence of serum, a number of compounds showed significant and selective cytotoxicity, suggesting that this set of compounds indeed bind serum proteins, which interfere with their ability to penetrate the cells (Table 3).

From the cytotoxicity results (Table 3) it was found that compounds **17a** and **17b** with unsubstituted indole and R^3 as phenyl and *p*-tolyl groups were inactive. Replacement of a phenyl moiety in **17a** with a benzyl substituent led to compound **17h** with selective cytotoxicity against HeLa cells (IC_{50} = 9.51 μM). Analogue **17i** having 5-methoxyindole and trimethoxyphenyl substituent was found to exhibit selective cytotoxic against the HEK293T cells (IC_{50} = 8.60 μM). Replacement of a 5-methoxyindole with 5-bromoindole (**17i** *vs* **17k**) was unfavorable for the activity. Interestingly, analogue **17l** with 5-fluoroindole and methoxyphenyl moieties found to be the most potent compound of the series and selectively cytotoxic towards HEK293T and HeLa cells with IC_{50} values of 12.10 and 3.41 μM, respectively. Introduction of additional methoxy groups in compound **17l**, resulted in an inactive analogue **17m**. Protection of an indole ring nitrogen with *p*-chlorobenzyl moiety led to compounds **17n-p** endowed with moderate activity against the tested cancer cell lines. As noted before, when the MTT assay was performed in the presence of FBS, only compound **17i** was found to exhibit selective cytotoxicity against HEK293T (IC_{50} = 8.74 μM) and HeLa (IC_{50} = 9.98 μM) cells. Compounds **17h**, **17k**, **17l** and **17n** showed moderate activity (IC_{50} = 32-41 μM) against the tested cell lines.

We next examined whether these compounds induce cytotoxicity by inducing apoptosis in cancer cell lines. As compound **17i** exhibited high potency in HeLa cells (IC_{50} = 9.98 μM), these cells were treated with **17i** for 24 h, fixed and stained with propidium iodide, and their nuclear morphology was analyzed using fluorescence microscopy. DMSO-treated cells were used as negative control and doxorubicin, which exerts cytotoxicity by promoting apoptosis, was used as a positive control. As shown in figure 5, nuclei in DMSO-treated HeLa cells retained their normal size and shape while HeLa cells treated with **17i** or doxorubicin showed large percentage of apoptotic nuclei, thereby confirming that **17i** indeed induces apoptosis in HeLa cells.

Comparison of antibacterial and anticancer activities of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** yielded either very specific antibacterial agents or anticancer agents or analogues possessing both activities. Analogue **17l**, which displayed high potency and specificity for HEK293T and HeLa cells, was largely ineffective as antibacterial agent both in Gram-positive and Gram-negative bacteria, suggesting that **17l** likely targets specific mammalian protein(s), which may be key to survival in these cells. Similarly, analogue **17h** was extremely specific and potent for HeLa cells, but did not affect other cancer cell lines even at 100 μM concentration. This compound displayed minimal activity in Gram-positive and Gram-negative bacteria as well, further underscoring its specificity towards mammalian targets. On the other hand, analogue **17i**, which too was highly potent against HEK293T and HeLa cells, but not against other cell lines, was among the most effective antibacterial agent

against Gram-negative bacteria. Importantly, **17i** was inactive against Gram-positive bacteria, suggesting it binds to specific targets in Gram-negative bacteria. It would be interesting to identify these proteins in *E. coli* and *P. putida* and analyze whether their orthologues exist in mammalian cells particularly in HEK293T and HeLa cells. We also identified **17o** to be potent and active against Gram-negative bacteria, but was completely inactive in mammalian cells. Thus, our library of compounds offer either highly specific antibacterial agents or equally specific anticancer agents and analogues which target both the species. This set of compounds provide an opportunity to dissect the drug mechanism which is either conserved across diverse species, or has diverged to specifically target one species in the presence of other.

In summary, we synthesized a diverse series of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** from the initial reaction of thioamides and bromopyruvic acid to afford thiazole carboxylic acids **16**, which were coupled with appropriate arylamines. Antibacterial study of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides led to identified **17i-k** and **17o** as potent compounds against Gram-negative bacteria, *P. putida* bacterial strain (MIC = 12.5 μg/mL). Moreover, *in vitro* cytotoxicity study of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides were resulted in **17i** and **17l** as the most potent compounds of the series. Our preliminary mechanism of action studies further indicated that thiazole carboxamide **17i** induces apoptosis in HeLa cells. Overall, these results suggest that appropriate substituents in indole and arylamide moieties of (3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p** are crucial for their targeted selectivity and potency for their antibacterial as well anticancer activities. Further, it may be necessary to perform MTT or XTT assays for testing potential cytotoxicity of test compounds both in the absence and presence of FBS to rule out any interference from serum binding proteins which may drastically impact cellular availability. Importantly, analogues **17h** and **17l** not only displayed high specificity among the cancer cell lines, they were also largely ineffective as antibacterial agents. In contrast, **17i** was highly potent in HeLa cells and Gram-negative bacteria, but inactive in other cancer cell lines and Gram-positive bacteria, suggesting that 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides display a broad range of bioactivities. As exemplified by our SAR studies, this series of compounds are very versatile and can be exploited to develop either highly specific and potent antibacterial agents or anticancer agents, or if required both of these properties could be incorporated in the same molecule. Finally, it would be important to identify their targets in bacteria and human cell lines to uncover their molecular mechanism, which in turn can be exploited to develop potential therapeutic interventions against various human diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the financial support from DBT, New Delhi (DK) and NIH R03 CA166912-2 (KS).

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25. General procedure for the synthesis of thiazole carboxamide (**17a-p**). To a mixture of thiazole carboxylic acid **16** (0.8 mmol) in dry THF (3 mL) was added EDCI.HCl (0.9 mmol), HOBt (0.9 mmol) and triethylamine (1.6 mmol) and stirred at 25 °C for 30 min. Arylamine (0.8 mmol) was added and resulting mixture was stirred for 10 h at 25 °C. Upon completion of reaction as indicated by TLC, solvent was evaporated in vaccuo, water was added (15 mL) and extracted with ethyl acetate (2 × 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield crude product which was purified through column chromatography to afford pure thiazole carboxamides **17a-p** in 78-87% yields.Spectral data for selected compounds: 2-(1H-Indol-3-yl)-N-phenylthiazole-4-carboxamide (**17a**). Yield 80%; off white solid; M.p 206-208 °C; IR (KBr, v cm^{-1}): 3348, 3263, 1666, 1597, 1545, 1435, 1126, 741, 687; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 10.11 (s, 1H), 8.35–8.26 (m, 3H), 7.87 (d, J = 7.8 Hz, 2H), 7.54 (dd, J = 5.9, 3.1 Hz, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.27 (dd, J = 6.0, 3.1 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.3, 159.3, 149.5, 138.3, 136.6, 128.6, 127.6, 124.0, 124.0, 122.5, 121.4, 121.0, 120.6, 120.4, 112.2, 109.9; ESI(FAB) m/z calcd for $C_{18}H_{13}N_3NaOS$: 342.07 $(M + Na)^+$, found 342.05. 2-(1H-Indol-3-yl)-N-p-tolylthiazole-4-carboxamide (**17b**). Yield 82%; pale yellow solid; M.p 221-223 °C; IR (KBr, v cm^{-1}): 3340, 3256, 1666, 1548, 1242, 1126, 810, 741, 671; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.03 (s, 1H), 8.31 (dd, J = 6.3, 2.7 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.24 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.54–7.50 (m, 1H), 7.28–7.24 (m, 2H), 7.20 (d, J = 8.3 Hz, 2H), 2.30 (s, 3H).; ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.7, 159.6, 150.1, 137.1, 136.3, 133.4, 129.5, 128.1, 124.5, 123.0, 121.7, 121.5, 121.0, 120.9, 112.7, 110.4, 21.0.; ESI(FAB) m/z calcd for $C_{19}H_{16}N_3OS$: 334.10 $(M + H)^+$, found 334.05. 2-(1H-indol-3-yl)-N-(4-methoxyphenyl)thiazole-4-carboxamide (**17c**). Yield 80%; off white solid; M.p 200-202 °C; IR (KBr, v cm^{-1}): 3364, 3232, 1666, 1512, 1242, 1111, 748, 617; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.02 (s, 1H), 8.36–8.29 (m, 1H), 8.28 (d, J = 2.6 Hz, 1H), 8.23 (s, 1H), 7.77 (s, 2H), 7.55–7.51 (m, 1H), 7.29–7.22 (m, 2H), 6.97 (d, J = 9.0 Hz, 2H), 3.76 (s, 3H).; ^{13}C NMR (75 MHz, DMSO d_6) δ 163.3, 159.0, 155.8, 149.7, 136.6, 131.3, 127.6, 124.0, 122.5, 122.3, 121.0, 121.0, 120.4, 113.8, 112.2, 109.9, 55.2.; ESI(FAB) m/z calcd for $C_{19}H_{14}N_3O_2S$: 348.09 $(M - H)^+$, found 348.15. N-(3,4-Dimethoxyphenyl)-2-(1H-indol-3-yl)thiazole-4-carboxamide (**17d**). Yield 79%; off white solid; M.p 176-178 °C; IR (KBr, v cm^{-1}): 3340, 3132, 1643, 1520, 1458, 1219, 1018, 741, 633; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.99 (s, 1H), 8.29 (s, 2H), 8.23 (s, 1H), 7.54 (dd, J = 6.8, 3.2 Hz, 2H), 7.43 (d, J = 7.1 Hz, 1H), 7.26 (dd, J = 5.8, 2.9 Hz, 2H), 6.97 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H).; ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3, 159.0, 149.7, 148.5, 145.4, 136.6, 131.8, 127.5, 124.0, 122.5, 121.1, 121.0, 120.3, 112.7, 112.3, 111.9, 111.0, 105.9, 69.7, 55.7, 55.5.; ESI(FAB) m/z calcd for $C_{20}H_{16}N_3O_3S$: 378.10 $(M - H)^+$, found 378.20.

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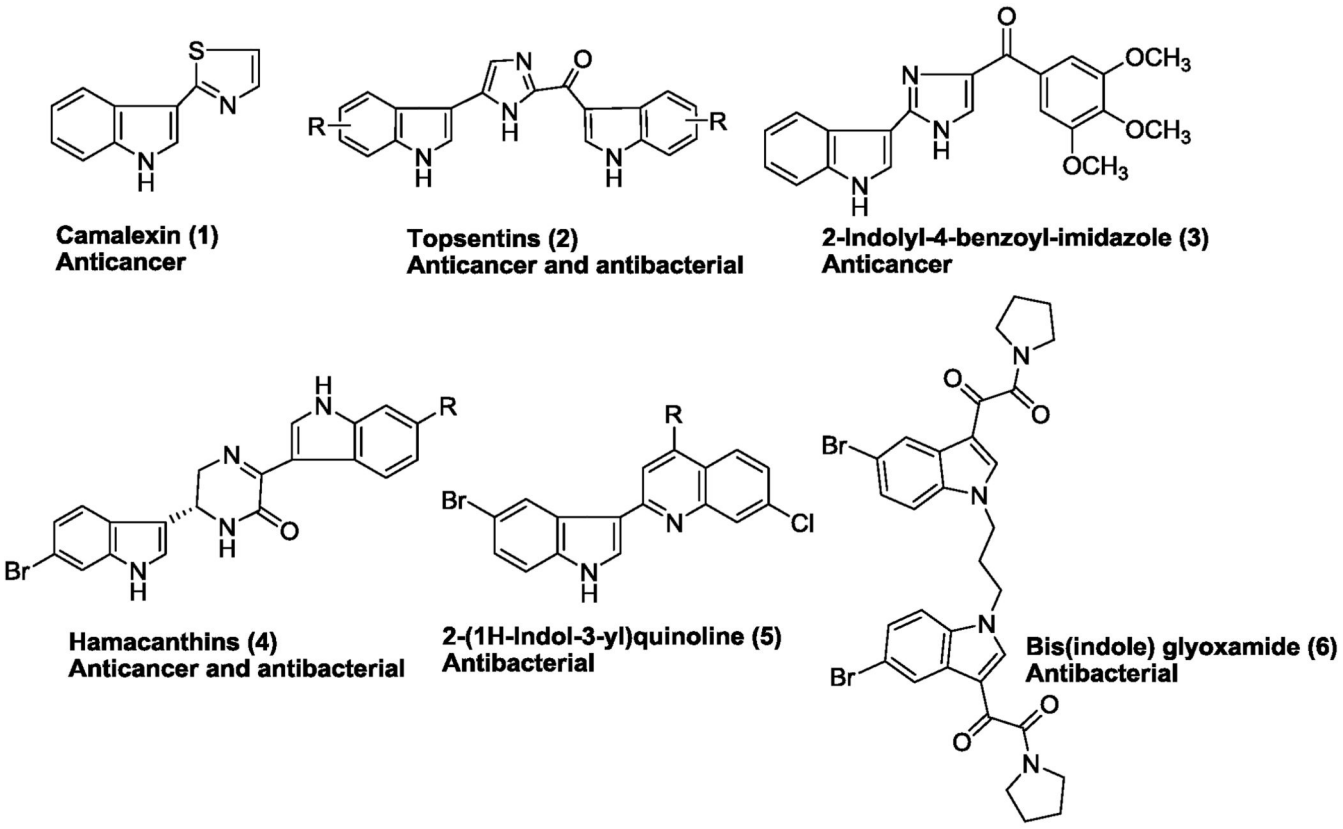


Figure 1.
Representative indole-based antibacterial and anticancer agents

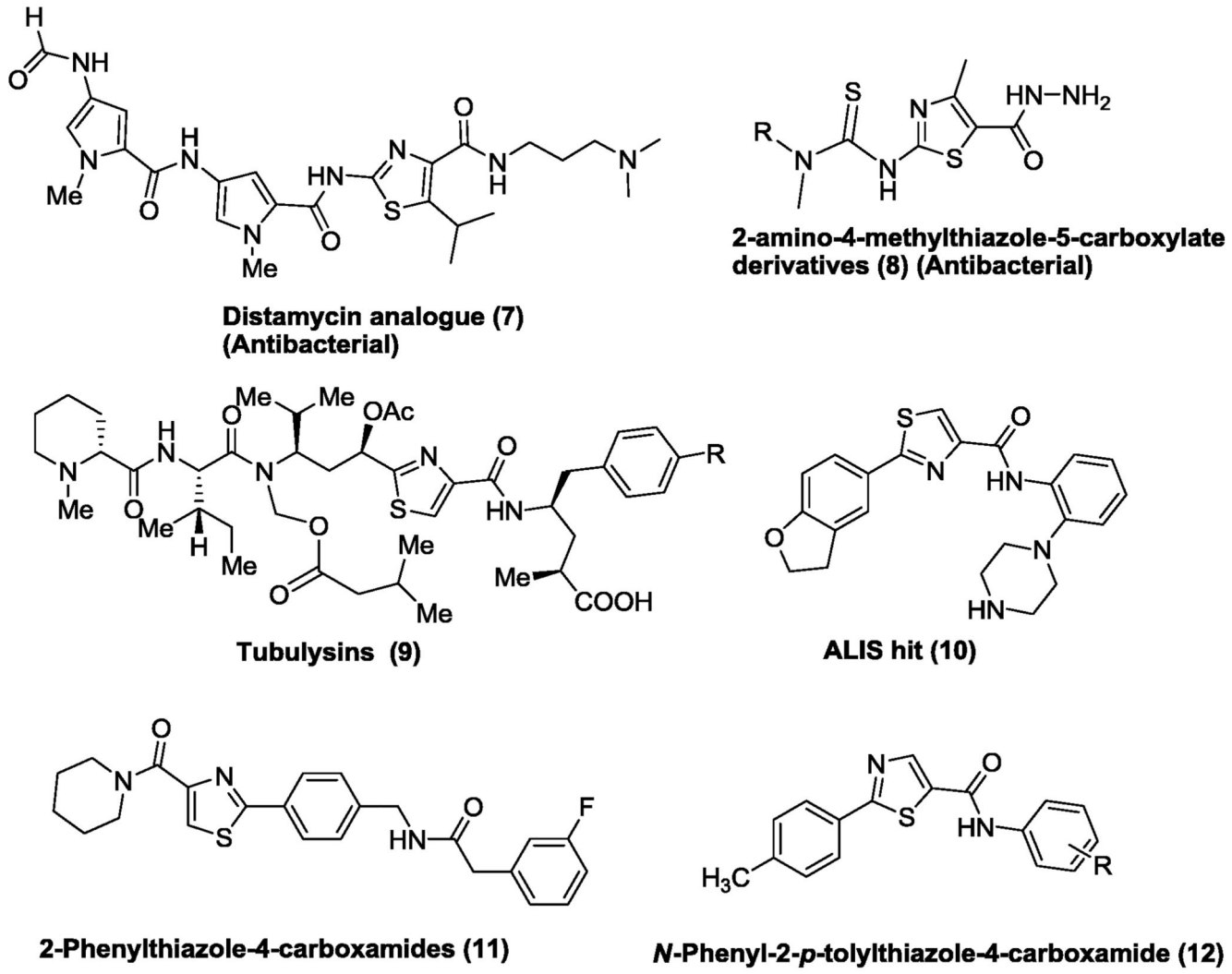


Figure 2.
Antibacterial and anticancer agents with thiazole-carboxamide scaffold

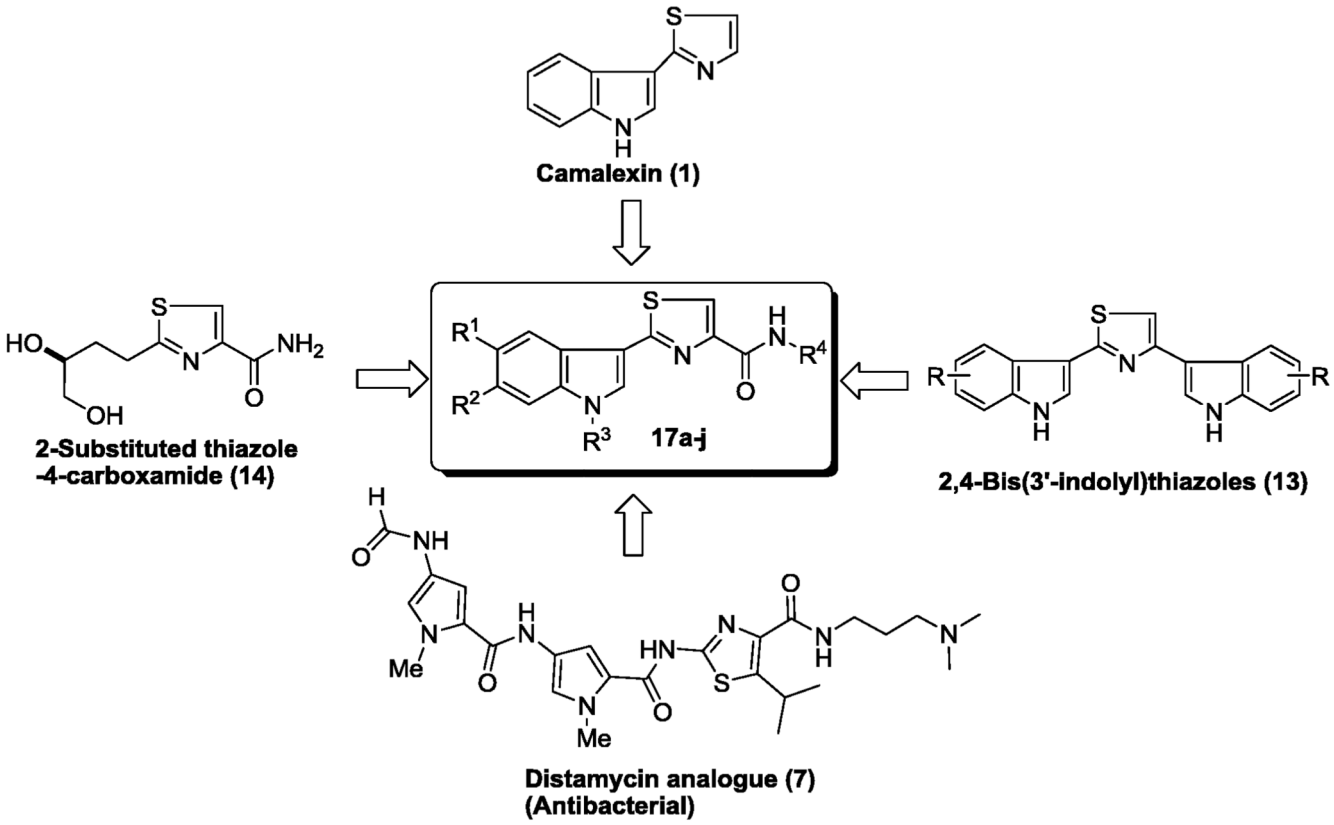


Figure 3.
Rational approach to 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p**

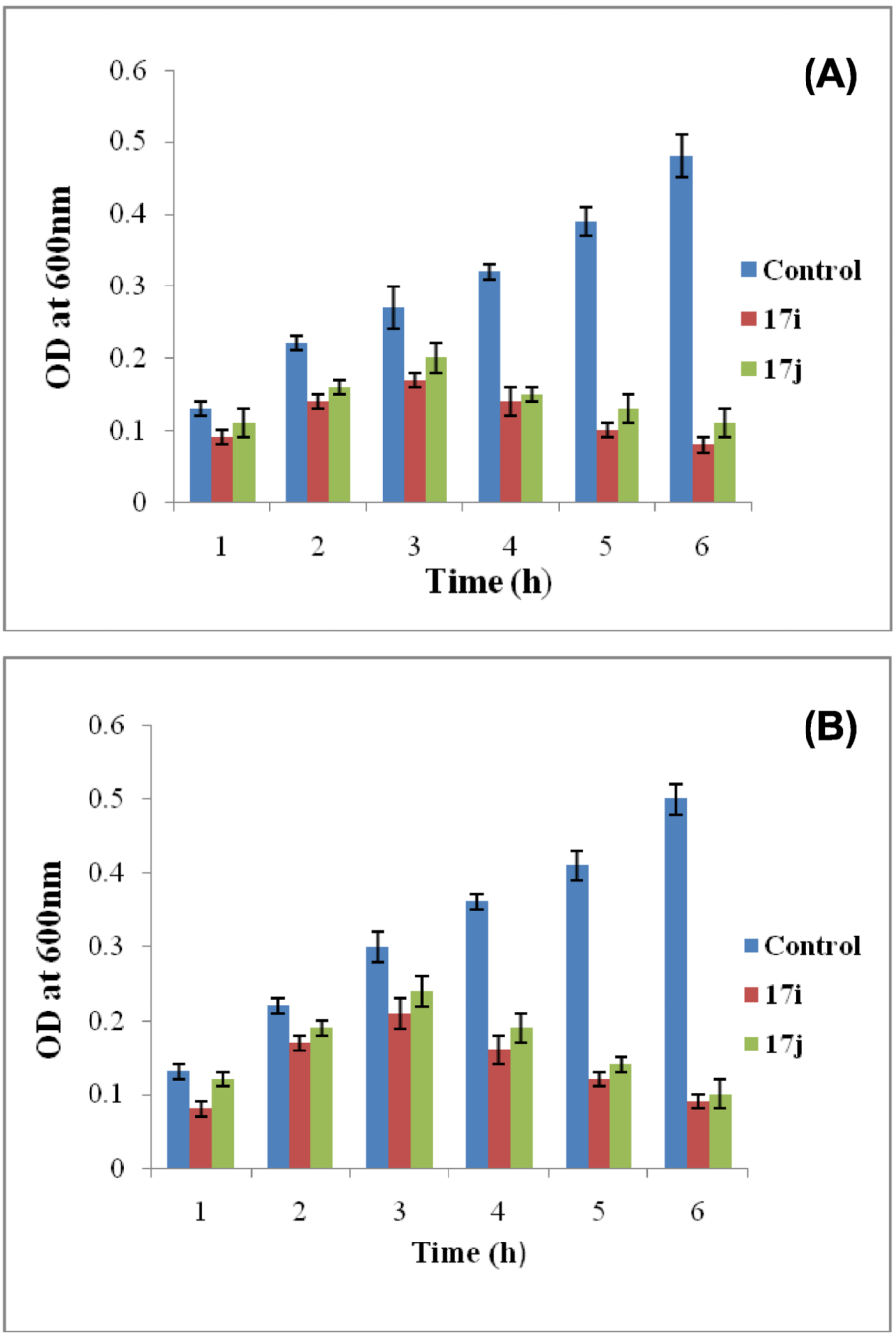


Figure 4.

Time dependent killing of (A) *E.coli* and (B) *P.putida* upon treated with compounds **17i** and **17j** at 4×MIC

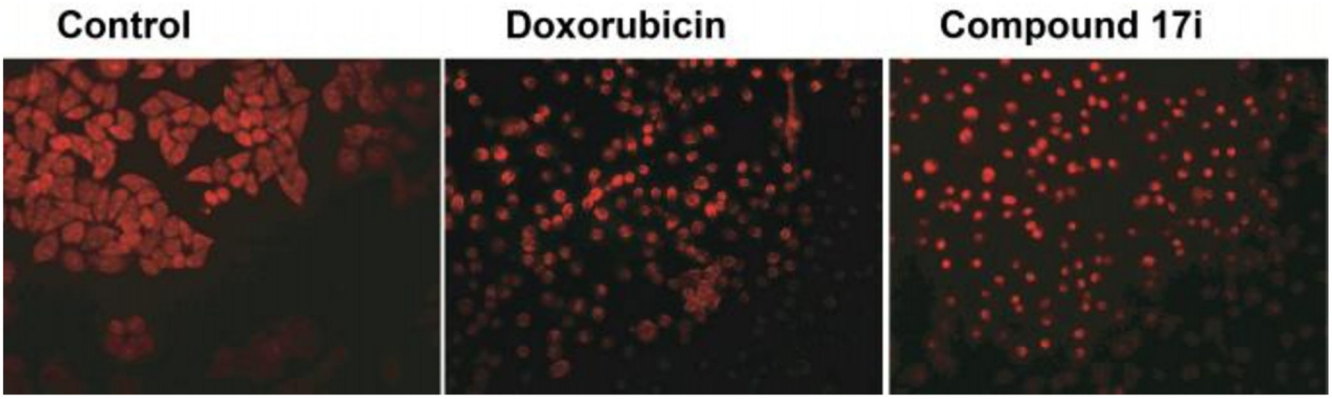
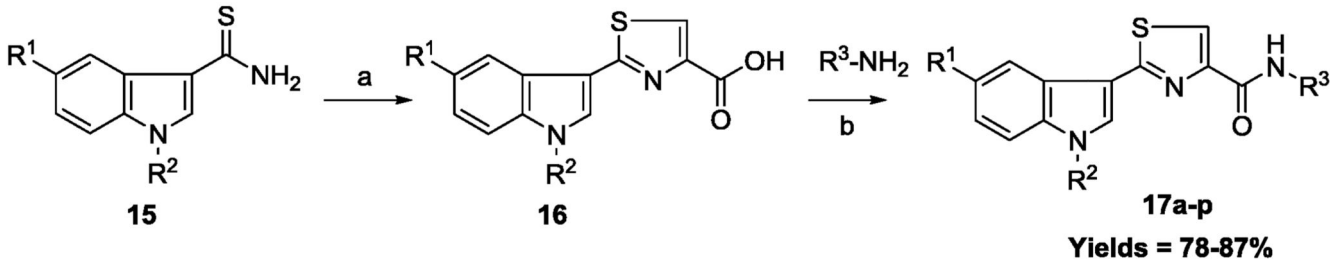


Figure 5.
Propidium iodide staining of HeLa cell treated with compound **17i** for 48 h. DMSO was used as a control.



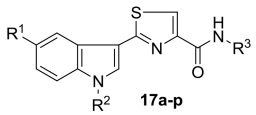
Scheme 1.

Reagents and conditions: (a) Bromopyruvic acid, 1,4-dioxane, 100 °C, 2 h; (b) EDCI.HCl, HOBt, NEt_3, THF, rt, 10 h.

Bioorg Med Chem Lett. Author manuscript; available in PMC 2016 October 01.

Table 1

In vitro antibacterial activity of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a–p**



17a-p

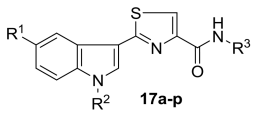
ZOI (mm) and MIC (μg/mL) values

Compound				Gram-positive bacteria				Gram-negative bacteria			
				S. auresus		*B. cereus*		*E. coli*		*P. putida*	
	R^1	**R^2**	**R^3**	**ZOI**	**MIC**	**ZOI**	**MIC**	**ZOI**	**MIC**	**ZOI**	**MIC**
17a	H	H	C_6H_5	14	**50**	-	-	13	100	13	100
17b	H	H	4-$CH_3C_6H_4$	-	-	-	-	12	100	12	100
17c	H	H	4-$CH_3OC_6H_4$	11	100	12	100	**14**	**50**	12	100
17d	H	H	3,4-$(CH_3O)_2C_6H_3$	14	50	14	50	**16**	**25**	16	25
17e	H	H	3,4,5-$(CH_3O)_3C_6H_2$	12	100	14	50	14	50	13	100
17f	H	H	4-FC_6H_4	12	100	10	100	13	100	12	100
17g	H	H	4-$(CH_3)_2NC_6H_4$	13	100	14	50	12	100	14	50
17h	H	H	$CH_2C_6H_5$	-	-	-	-	13	100	13	100
17i	OCH_3	H	3,4,5-$(CH_3O)_3C_6H_2$	13	100	14	50	**18**	**12.5**	**18**	**12.5**
17j	Br	H	4-$CH_3OC_6H_4$	14	50	15	50	**15**	**12.5**	**16**	**12.5**
17k	Br	H	3,4,5-$(CH_3O)_3C_6H_2$	**15**	**50**	**16**	**12.5**	**14**	**50**	**16**	**12.5**
17l	F	H	4-$CH_3OC_6H_4$	12	100	13	100	14	50	13	100
17m	F	H	3,4,5-$(CH_3O)_3C_6H_2$	12	100	10	100	14	50	14	50
17n	H	4-$ClC_6H_4CH_2$	C_6H_5	12	100	13	100	15	50	15	50
17o	H	4-$ClC_6H_4CH_2$	4-$CH_3OC_6H_4$	14	100	15	50	**16**	**12.5**	**16**	**12.5**
17p	H	4-$ClC_6H_4CH_2$	3,4,5-$(CH_3O)_3C_6H_2$	13	100	12	100	15	50	14	100
Ciprofloxacin				23	6.25	24	6.25	23	6.25	21	12.5

The zone of inhibition and MIC values for compounds with significant activity are shown in bold

Table 2

In vitro cytotoxicity (with FBS) of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p**



17a-p

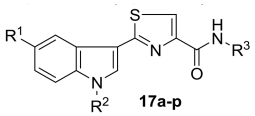
				$IC_{50}(\mu M)^{a,b}$					
Compd	**R^1**	**R^2**	**R^3**	**HEK 293T**	**C4-2**	**HeLa**	**PC3**	**MDA-MB-231**	**LNCaP**
17a	H	H	C_6H_5	>100	>100	>100	>100	>100	>100
17b	H	H	4-$CH_3C_6H_4$	>100	>100	>100	>100	>100	>100
17h	H	H	$CH_2C_6H_5$	74.50±1.19	>100	41.38±2.03	>100	>100	>100
17i	OCH_3	H	3,4,5-$(CH_3O)_3C_6H_2$	**8.74±1.26**	>100	**9.98±0.01**	>100	>100	84.80±1.21
17k	Br	H	3,4,5-$(CH_3O)_3C_6H_2$	32.82±0.75	>100	93.03±3.96	>100	>100	>100
17l	F	H	4-$CH_3OC_6H_4$	>100	>100	33.48±0.98	>100	>100	75.42±1.88
17m	F	H	3,4,5-$(CH_3O)_3C_6H_2$	66.02±3.28	>100	48.85±1.35	>100	>100	88.51±3.25
17n	H	4-$ClC_6H_4CH_2$	C_6H_5	>100	>100	32.07±0.87	>100	>100	68.94±2.49
17o	H	4-$ClC_6H_4CH_2$	4-$CH_3OC_6H_4$	>100	>100	90.85±3.73	>100	>100	>100
17p	H	4-$ClC_6H_4CH_2$	3,4,5-$(CH_3O)_3C_6H_2$	>100	>100	>100	>100	>100	>100
	Doxorubicin			0.75±0.03	0.57±0.08	0.43±0.10	9.8±0.40	6.29±0.24	7.40±1.10

[a] IC_{50} values are the mean of three different experiments performed in duplicate;

[b] **17c-g** and **17j**: ND

Table 3

In vitro cytotoxicity (without FBS) of 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides **17a-p**



17a-p

				IC_{50} (μM)[a]					
Compd	**R^1**	**R^2**	**R^3**	**HEK 293T**	**C4-2**	**HeLa**	**PC3**	**MDA-MB-231**	**LNCaP**
17a	H	H	C_6H_5	41.07±2.64	>100	>100	>100	79.37±3.98	>100
17b	H	H	4-$CH_3C_6H_4$	>100	>100	>100	>100	>100	>100
17h	H	H	$CH_2C_6H_5$	>100	>100	**9.51±0.22**	>100	>100	>100
17i	OCH_3	H	3,4,5-$(CH_3O)_3C_6H_2$	**8.60±0.91**	>100	29.64±1.44	94.34±2.04	>100	>100
17k	Br	H	3,4,5-$(CH_3O)_3C_6H_2$	>100	>100	55.79±4.73	>100	>100	>100
17l	F	H	4-$CH_3OC_6H_4$	**12.10±0.61**	>100	**3.41±0.07**	>100	49.41±5.91	66.41±4.94
17m	F	H	3,4,5-$(CH_3O)_3C_6H_2$	>100	>100	>100	89.00±0.81	>100	>100
17n	H	4-$ClC_6H_4CH_2$	C_6H_5	>100	>100	24.27±2.93	76.40±3.22	50.51±4.92	64.07±4.16
17o	H	4-$ClC_6H_4CH_2$	4-$CH_3OC_6H_4$	>100	>100	>100	>100	84.90±2.38	>100
17p	H	4-$ClC_6H_4CH_2$	3,4,5-$(CH_3O)_3C_6H_2$	58.69±1.90	>100	91.39±3.31	>100	>100	97.70±1.76
	Doxorubicin			0.84±0.05	1.02±0.06	0.45±0.06	7.65±0.11	6.03±0.22	6.46±0.09

[a] IC_{50} values are the mean of three different experiments performed in duplicate