Journal Pre-proof

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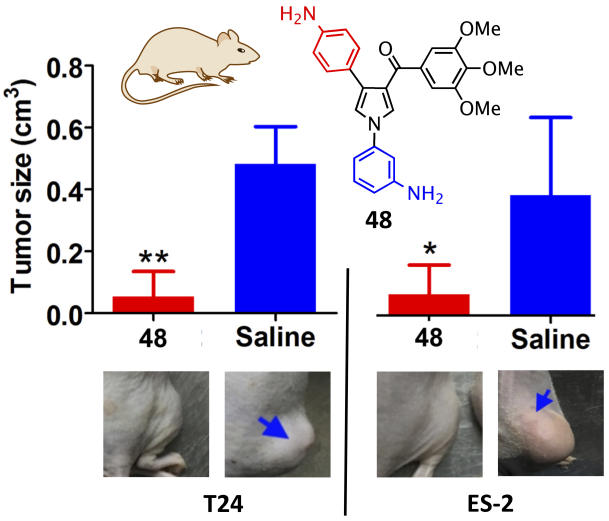

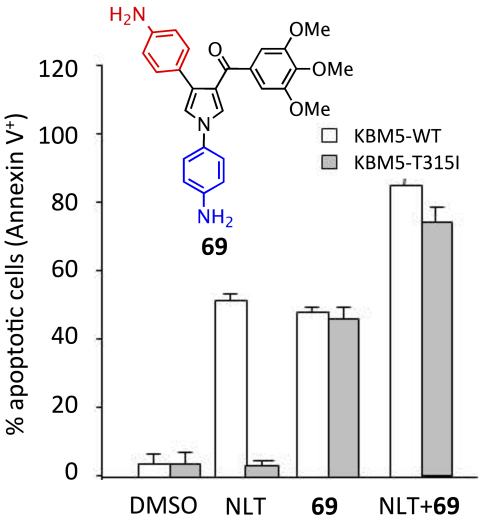

Structure-Activity Relationship Studies and *in Vitro* and *in Vivo* Anticancer Activity of Novel 3□Aroyl-1,4-diarylpyrroles against Solid Tumors and Hematological Malignancies

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ABSTRACT

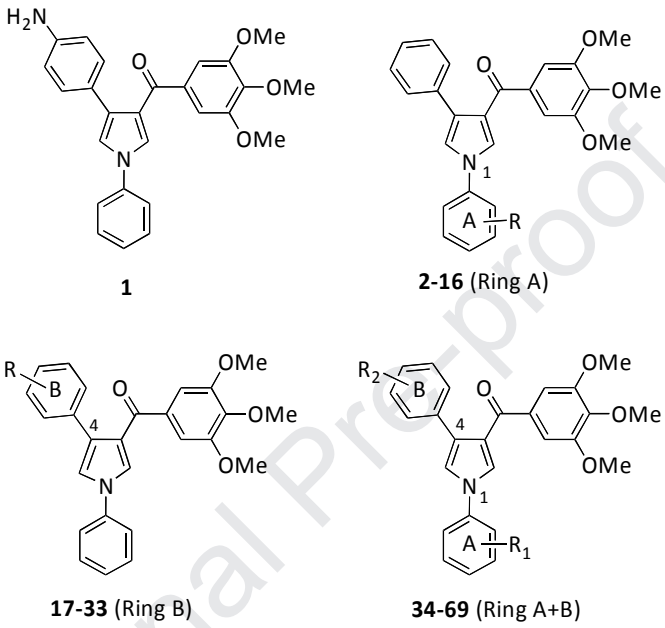
Novel 3-aroyl-1,4-diarylpyrrole derivatives were synthesized to explore structure-activity relationships at the phenyls at positions 1 and 4 of the pyrrole. The presence of amino phenyl rings at positions 1 and 4 of the pyrrole ring were found to be a crucial requirement for potent antitumor activity. Several compounds strongly inhibited tubulin assembly through binding to the colchicine site. Compounds **42**, **44**, **48**, **62** and **69** showed antitumor activity with low nanomolar IC_{50} values in several cancer cell lines. Compound **48** was generally more effective as an inhibitor of glioblastoma, colorectal and urinary bladder cancer cell lines; **69** consistently inhibited CML cell lines and demonstrated superiority in nilotinib and imatinib resistant LAMA84-R and KBM5-T315I cells. In animal models, compound **48** exhibited significant inhibition of the growth of T24 bladder carcinoma and ES-2 ovarian clear cell carcinoma tumors. Compounds **48** and **69** represent robust lead compounds for the design of new broad-spectrum anticancer agents active in different types of solid and hematological tumors.

1. Introduction

Cancer is a serious leading cause of death worldwide, claiming more than 8.2 million human lives in 2012. According to available global cancer statistics, lung (12.3%), breast (12.3%), colorectal (10.6%) and prostate (7.5%) account for the most cancers diagnosed worldwide. Nevertheless, leukemia alone represents 2.5 % of all diagnosed cancers [1,2]. Cancer cells are characterized by a high rate of cell division. Microtubules (MTs) play a key role in regulating the eukaryotic cell machinery.[3] Interfering with the MT dynamic equilibrium is an attractive option for the design of effective agents against a wide variety of cancers [4-11].

We recently reported the synthesis of (4-(4-aminophenyl)-1-phenyl-1*H*-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**1**) (Chart 1), an inhibitor of tubulin polymerization and MCF-7 cancer cell growth with antiproliferation activity in BCR/ABL-expressing chronic myeloid leukemia (CML) cells from patients in blast crisis [12]. Herein we report the synthesis and structure-activity relationship (SAR) studies of new 3-aroyl-1,4-diarylpyrrole (ARDAP) compounds **2-69**. The SAR studies have been grouped in three series of derivatives based on the substituents (*i*) at the pyrrole 1-phenyl ring (Ring A, **2-16**), (*ii*) at the 4-phenyl ring (Ring B, **17-33**), and (*iii)* at both these phenyl rings (Rings A+B, **34-69**). We examined their effects as inhibitors of tubulin polymerization and MCF-7 breast cancer cell growth and as inhibitors of the binding of colchicine to tubulin (Tables 1-3). Five highly potent derivatives, **42**, **44**, **48**, **62** and **69**, were evaluated in a panel of cancer cell lines, including leukemia (KU812, LAMA84-S, LAMA84-R, KBM5-WT, KBM5-T315I), glioblastoma (T98G, U87MG and U343MG), neuroblastoma (SK-N-BE and SK-N-BE(2)-C), colorectal (HT29, HCT116, SW480 and SW620) and urinary bladder (T24) cells. ARDAPs **42**, **44**, **48**, **62** and **69** demonstrated broad spectrum activity in all these cell lines, with **48** generally more effective in the glioblastoma, colorectal

and urinary bladder cancer cells and **69** in the leukemia cell lines. In animal models, compound **48** exhibited significant inhibition of the growth of the T24 bladder and ES-2 ovarian clear cell carcinoma tumors.



1 **2-16** (Ring A) **17-33** (Ring B) **34-69** (Ring A+B)

Chart 1. General structures of ARDAP compounds **1**, **2-16** (Table 1), **17-33** (Table 2 and **34-69** (Table 3).

2. Chemistry

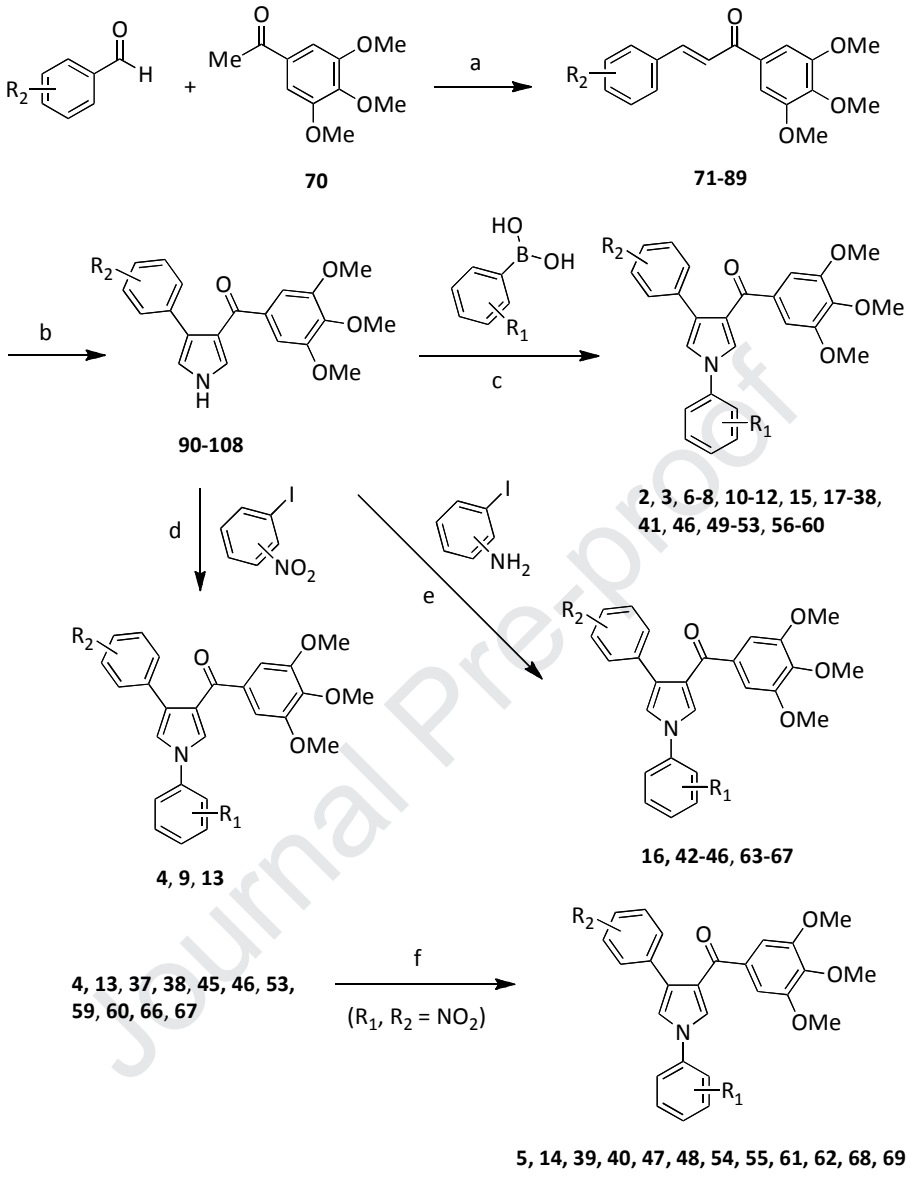
2.1. Synthetic procedures

The new ARDAP derivatives were synthesized as depicted in Scheme 1. Reaction of an appropriate benzaldehyde with 3,4,5-trimethoxyacetophenone (**70**) in the presence of NaOH in ethanol at room temperature for 24 or 2 h afforded chalcones **71-84** and **85-89**, respectively, which underwent cyclization into the corresponding pyrrole derivatives **90-108** with *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of NaH in dimethyl sulfoxide and diethyl ether at room temperature. In order to improve yield, pyrroles **90-108** were transformed

into ARDAP compounds by different procedures: (*i*) with an appropriate boronic acid in the presence of copper(II) acetate and triethylamine in dichloromethane under an Ar stream at room temperature (**2**, **26**, **30** and **33**), at 40 °C (**3**, **7**, **24**, **58**) or at 50 °C (**17-23**, **25**, **27-29**, **31**, **32**, **34-38**, **41**, **49-53**, **56, 57, 59 and 60**) for 18 h, or in 1,2-dichloroethane at 80 °C for 24 h (**8**, **10-12** and **15**); for compound **6**, pyridine in dichloromethane was used instead of triethylamine at room temperature for 5 h; (*ii*) with an appropriate iodonitrobenzene, copper(I) bromide, cesium carbonate and 8-quinolinol *N*-oxide in dimethyl sulfoxide at 65 °C for 18 h (**4**, **9** and **13**); (*iii*) with an appropriate iodoaniline, copper(I) iodide, cesium carbonate, 1,10-phenanthroline in 1,4-dioxane at 110 °C for 24 h (**42-46** and **63-67**); for **16**, DMF at 110 °C overnight was used. Reduction of nitro derivatives **4, 13**, **37, 38**, **45, 46**, **53, 59**, **60, 66**, **67** with tin(II) chloride dehydrate in ethyl acetate at 80 °C for 3 h furnished amino ARDAPs **5**, **14**, **39**, **4**, **47, 48**, **54**, **55, 61, 62**, **68** and **69**.

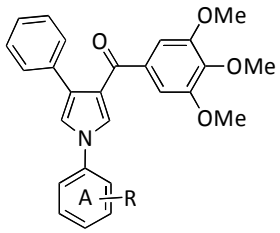
2.2 Molecular modeling studies

The binding modes of compounds **42, 44, 48, 62 and 69** were evaluated by docking experiments using our previously reported procedure [12]. The proposed docking poses were consistent across all inspected structures and were superimposable with the bound DAMA-colchicine (pdb code: 1SA0) [13]. Inspection of the binding mode highlighted the following key contacts: (*i*) the trimethoyphenyl ring formed polar contacts with the Cys241β side chain and hydrophobic interactions with Leu248β and Leu255β; (*ii*) the B ring was involved in hydrophobic contacts with the Lys352β side chain and π-cation interactions with the Lys352 ε-nitrogen atom; (*iii)* the A ring formed hydrophobic interactions with Met259β, Lys353β, Ala 180α and Val181α. The position of the substituent of both the A and B rings did not affect the binding mode (Figure 1SD, supplementary data).

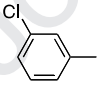
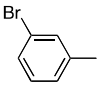
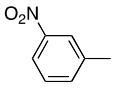
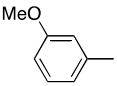
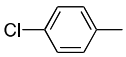
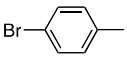
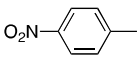


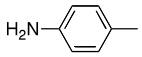
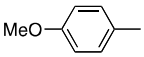
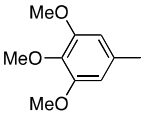
Scheme 1. Synthesis of compounds **2-69**. For structures **2-69**, see Tables 1-3. Compounds **71-108**, R_2: H, **71**, **90**; 2-Me, **85**, **91**; 2-Cl, **72**, **92**; 3-Cl, **86**, **93**; 4-Cl, **73**, **94**; 2-Br, **74**, **95**; 3-Br, **75**, **96**; 4-Br, **76**, **97**; 2-NO_2, **77**, **98**; 3-NO_2, **78**, **99**; 4-NO_2, **79**, **100**; 2-MeO, **87**, **101**; 3-MeO, **88**, **102**; 4-MeO, **80**, **103**; 5-Br,2-MeO, **81**, **104**; 2,5-F_2, **82**, **105**; 2,4,6-F_3, **89**, **106**; styryl, **83**, **107**; 2-F, **84**, **108**. Reagents and reaction conditions: (a) appropriate benzaldehyde, NaOH, EtOH 96%; r.t., 24 h (**71-84)** or 2 h (**85-89)**; (b) NaH, TosMIC, DMSO/Et_2O, r.t., 4 h (**90-108**); (c) appropriate boronic acid, $Cu(OAc)_2$, Et_3N, DCM, r.t., 18 h (**2**, **26**, **30**, **33**), DCM, 40 °C, 18 h (**3**, **7**, **24**, **58**), DCE, 50 °C, 18 h (**17-23**, **25**, **27-29**, **31**, **32**, **34-38**, **41**, **49-53**, **56, 57, 59 and 60**), DCE, 80 °C, 18 h, (**8**, **10-12**, **15**), Pyr, DCM, r.t., 5 h (**6**); (d) appropriate iodonitrobenzene, CuBr, 8-quinolinol *N*-oxide, Cs_2CO_3, DMSO, 65 °C, 18 h (**4**, **9**, **13**); (e) appropriate iodoaniline, CuI, Cs_2CO_3, 1,10-phenanthroline, dioxane, 110 °C , 24 h (**42-46**, **63-67**), 110 °C, DMF, overnight (**16)**; (f) $SnCl_2{\cdot}2H_2O$, MeCOOEt, 80 °C, 3 h (**5**, **14**, **39**, **4**, **47, 48**, **54**, **55, 61, 62**, **68** and **69**).

Table 1
Inhibition of tubulin polymerization, growth of MCF-7 human breast carcinoma cells and colchicine binding to tubulin by compounds **2-16**.[a]



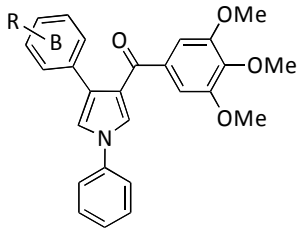
2-16

Compd	Ph-R (A ring)	IC_{50} ± SD (μM)	IC_{50} ± SD (nM)	(% ± SD)
		Tubulin[b]	MCF-7[c]	Inh. colch. bind.[d]
2		>20[e]	2200 ± 50	nd[e]
3		>20	1800 ± 200	nd
4		>20	5000 ± 0	nd
5		>20	3800 ± 400	nd
6		1.3 ± 0.01	150 ± 20	22 ± 4
7		2.1 ± 0.2	150 ± 4	37 ± 4
8		1.9 ± 0.04	78 ± 4	23 ± 4
9		>20	550 ± 70	12 ± 2
10		1.6 ± 0.04	500 ± 70	25 ± 2
11		1.7 ± 0.1	140 ± 40	42 ± 2
12		0.66 ± 0.1	20 ± 2	78 ± 4
13		3.3 ± 0.3	4000 ± 700	18 ± 3

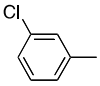
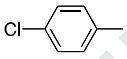
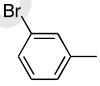
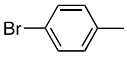
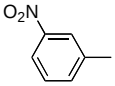
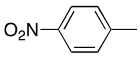
14		1.6 ± 0.1	35 ± 7	67 ± 1
15		0.96 ± 0.1	120 ± 10	27 ± 5
16		>20	>5000	6.5 ± 4

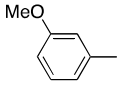
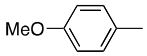
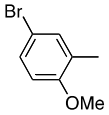
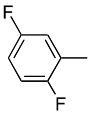
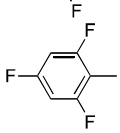
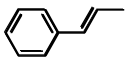
[a] Experiments were performed in duplicate or triplicate.
[b] Inhibition of tubulin polymerization. Tubulin was at 10 μM in the assembly assay.
[c] Inhibition of growth of MCF-7 human breast carcinoma cells.
[d] Inhibition of [^{3}H]colchicine binding: tubulin, [^{3}H]colchicine, inhibitor at 1:5:5 μM.
[e] nd, not done.

Table 2
Inhibition of tubulin polymerization, growth of MCF-7 human breast carcinoma cells and colchicine binding to tubulin by compounds **17-33**.[a]



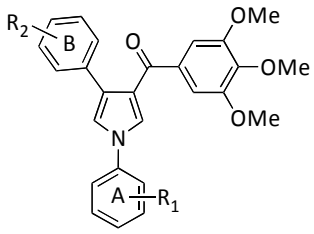
17-33

Compd	Ph-R (A ring)	IC_{50} ± SD (μM)	IC_{50} ± SD (nM)	(% ± SD)
		Tubulin[b]	MCF-7[c]	Inh. colch. bind.[d]
17		0.79 ± 0.1	190 ± 30	18 ± 1
18		0.63 ± 0.07	76 ± 8	50 ± 2
19		2.3 ± 0.04	540 ± 90	7.5 ± 0.3
20		1.2 ± 0.08	290 ± 10	23 ± 2
21		0.67 ± 0.1	190 ± 10	39 ± 1
22		>20	950 ± 70	nd[e]
23		0.77 ± 0.1	340 ± 60	14 ± 4
24		0.73 ± 0.1	49 ± 10	61 ± 1
25		0.94 ± 0.06	50 ± 10	12 ± 1
26		>20[f]	590 ± 20	nd

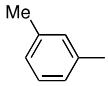
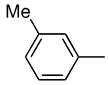
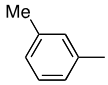
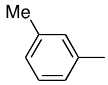
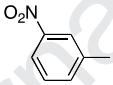
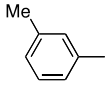
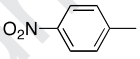
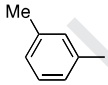
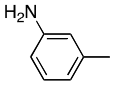
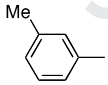
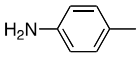
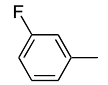
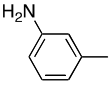
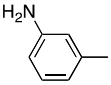
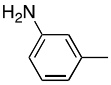
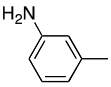
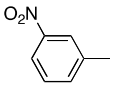
27		0.55 ± 0.08	190 ± 30	31 ± 2
28		0.45 ± 0.05	180 ± 30	27 ± 1
29		0.48 ± 0.04	70 ± 10	42 ± 0.2
30		>20	2200 ± 50	nd
31		1.3 ± 0.08	230 ± 40	24 ± 0.07
32		0.51 ± 0.1	180 ± 30	27 ± 1
33		>20	2200 ± 50	nd

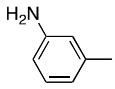
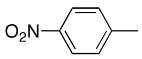
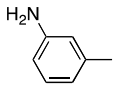
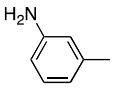
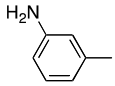
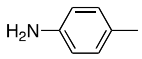
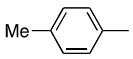
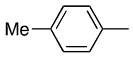
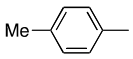
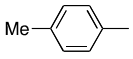
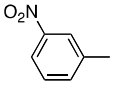
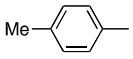
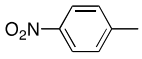
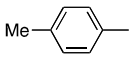
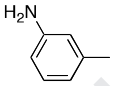
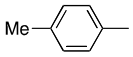
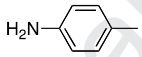
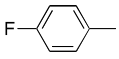
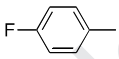
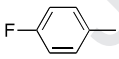
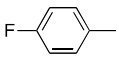
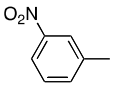
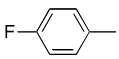
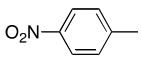
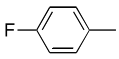
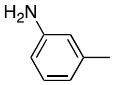
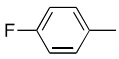
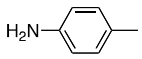
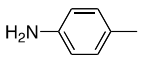
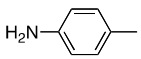
[a] Experiments were performed in duplicate or triplicate.
[b] Inhibition of tubulin polymerization. Tubulin was at 10 μM in the assembly assay.
[c] Inhibition of growth of MCF-7 human breast carcinoma cells.
[d] Inhibition of [^{3}H]colchicine binding: tubulin, [^{3}H]colchicine, inhibitor at 1:5:5 μM.
[e] nd, not done.

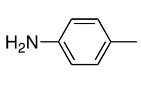
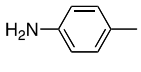
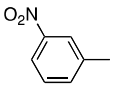
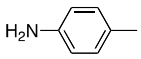
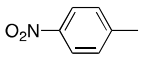
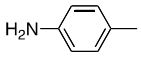
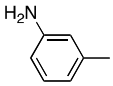
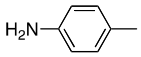
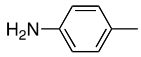
Table 3
Inhibition of tubulin polymerization, growth of MCF-7 human breast carcinoma cells and colchicine binding to tubulin by compounds **34-69**.[a]



34-69

Compd	Ph-R_1 (A ring)	Ph-R_2 (B ring)	IC_{50} ± SD (μM)	IC_{50} ± SD (nM)	(% ± SD)
			Tubulin[b]	MCF-7[c]	Inh. colch. bind.[d]
34			0.79 ± 0.04	190 ± 20	57 ± 4
35			0.71 ± 0.1	420 ± 30	39 ± 3
36			1.2 ± 0.06	220 ± 50	41 ± 9
37			>20	880 ± 40	4.2 ± 5
38			>20	780 ± 200	10 ± 0.8
39			0.91 ± 0.1	130 ± 30	64 ± 4
40			0.33 ± 0.02	18 ± 4	88 ± 0.4
41			1.1 ± 0.1	190 ± 10	41 ± 2
42			0.50 ± 0.02	17 ± 5	90 ± 1
43			0.63 ± 0.1	40 ± 4	79 ± 2
44			0.71 ± 0.02	14 ± 2	82 ± 0.2
45			1.7 ± 0.07	510 ± 80	32 ± 5

46			0.78 ± 0.1	110 ± 7	41 ± 2
47			0.88 ± 0.1	60 ± 7	70 ± 3
48			0.47 ± 0.03	14 ± 2	92 ± 0.07
49			0.78 ± 0.06	44 ± 9	80 ± 0.5
50			0.48 ± 0.04	180 ± 30	70 ± 3
51			0.61 ± 0.004	65 ± 7	71 ± 1
52			0.71 ± 0.07	210 ± 7	36 ± 5
53			0.65 ± 0.1	200 ± 40	34 ± 2
54			0.42 ± 0.01	53 ± 4	88 ± 0.3
55			0.36 ± 0.06	6.0 ± 2	95 ± 0.9
56			0.66 ± 0.1	39 ± 1	68 ± 4
57			0.51 ± 0.02	83 ± 10	65 ± 0.6
58			0.68 ± 0.1	38 ± 4	46 ± 0.04
59			>20	440 ± 60	11 ± 4
60			>20	240 ± 30	0
61			0.41 ± 0.02	53 ± 4	68 ± 2
62			0.50 ± 0.1	12 ± 3	90 ± 0.1
63			0.59 ± 0.1	28 ± 4	79 ± 1
64			0.71 ± 0.1	83 ± 10	65 ± 0.6

65			0.52 ± 0.01	53 ± 4	69 ± 0.6
66			3.8 ± 0.4	260 ± 60	18 ± 2
67			1.8 ± 0.3	260 ± 30	23 ± 5
68			0.87 ± 0.1	78 ± 4	59 ± 2
69			0.38 ± 0.04	15 ± 2	87 ± 0.09

[a] Experiments were performed in duplicate or triplicate.
[b] Inhibition of tubulin polymerization. Tubulin was at 10 μM in the assembly assay.
[c] Inhibition of growth of MCF-7 human breast carcinoma cells.
[d] Inhibition of [^{3}H]colchicine binding: tubulin, [^{3}H]colchicine, inhibitor at 1:5:5 μM. With the inhibitor at 1 μM, **42** yielded 68 ± 0.4, **48** 67 ± 2, **55** 74 ± 2, and **62** 61 ± 4 % inhibition.
[e] nd, not done.

3. Results and discussion

3.1. Inhibition of tubulin polymerization and MCF+7 cancer cell growth

*3.1.1. Compounds **2-16**, Ring A (Table 1).* We first synthesized ARDAP derivatives **2-16** to explore a variety of substituents at the 1-phenyl of the pyrrole nucleus (Table 1). As tubulin polymerization inhibitors, ARDAPs **6**, **8**, **10, 11** and **14** showed IC_{50} values in the 1.0-2.0 μM range, and two compounds, **12** and **15,** were inhibitory at submicromolar concentrations. With the exception of **6**, introduction of substituent at position 2 of the 1-phenyl ring abolished the ability of a compound to inhibit tubulin polymerization. Derivatives bearing a methoxy group at position 2, 3 or 4 of the 1-phenyl ring were all potent inhibitors of tubulin assembly (compare **6** (IC_{50} = 1.3 μM), **10** (IC_{50} = 1.6 μM) and **15** (IC_{50} = 0.96 μM). Among ARDAPs **2-16**, compound, **12** (IC_{50} = 0.66 μM) was the most potent tubulin polymerization inhibitor. In general, ARDAPs

bearing a substituent at position 4 of the 1-phenyl ring were superior to the corresponding 3-substituted counterparts (compare **11** with **7**, **12** with **8**, and **15** with **10**) in both biochemical and cellular assays. The 4-bromo- **12** (IC_{50} = 20 nM) and 4-amino- **14** (IC_{50} = 35 nM) phenyl derivatives were the most potent inhibitors of the growth of human MCF-7 nonmetastatic breast cancer epithelial cells among the ring A modified derivatives.

*3.1.2. Compounds **17-33**, Ring B (Table 2).* ARDAP derivatives **17-33** were synthesized to evaluate substituent on the 4-phenyl ring of the pyrrole nucleus (Table 2). Ten ARDAP derivatives, **17**, **18**, **21**, **23-25**, **27-29** and **32**, inhibited tubulin polymerization with IC_{50} values at submicromolar concentrations, and two compounds (**20** and **31**) had IC_{50} values in the 1.0-2.0 μM range. ARDAP derivatives bearing a chlorine or a bromine atom at position 2 or 4 of the 4-phenyl ring were more potent than the corresponding 3-substituted counterparts [compare **18** (IC_{50} = 0.63 μM) and **20** (IC_{50} = 1.2 μM) with **19** (IC_{50} = 2.3 μM); **21** (IC_{50} = 0.67 μM) and **23** (IC_{50} = 0.77 μM) with **22** (IC_{50} >20 μM)]. In contrast, ARDAPs **24** (IC_{50} = 0.73 μM) and **25** (IC_{50} = 0.94 μM), bearing a nitro group at position 2 or 3 of the 4-phenyl ring were much superior to the corresponding 4-nitro derivative **26** (IC_{50} >20 μM). Introduction of a methoxy group on any position of the 4-phenyl ring (ARDAPs **27-29**) yielded potent inhibitors of tubulin assembly, with IC_{50}'s of 0.55, 0.45 and 0.48 μM, respectively. Fluorine atoms at positions 2,5- (**31**, IC_{50} = 1.3 μM) or 2,4,6 (**32**, IC_{50} = 0.51 μM) of the 4-phenyl ring also resulted in potent tubulin polymerization inhibitors. Several derivatives inhibited MCF-7 cancer cell growth with high nanomolar IC_{50} values; compounds **18**, **24**, **25** and **29** were the most potent inhibitors of the MCF-7 cell growth in this group of derivatives, with IC_{50} values ranging from 49 (**24**) to 76 nM (**18**).

*3.1.3. Compounds **34-69**, Rings A+B (Table 3).* We synthesized compounds **34-69** to combine

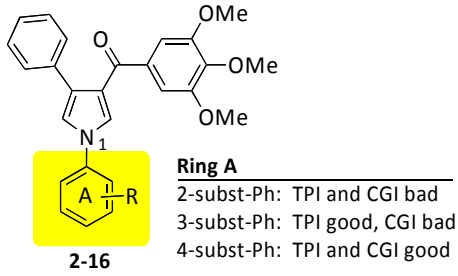
substituents at both the aryl rings at position 1 (Ring A) and position 4 (Ring B) of the pyrrole nucleus (Table 3). New ARDAPs with substituents at position 2 of the 1-phenyl ring were synthesized because of the weak activity displayed by derivatives **2-6** (Table 1). Many of these derivatives (**34**, **35**, **39**, **40**, **42-44**, **46-58**, **61-65**, **68** and **69**) inhibited tubulin polymerization with submicromolar IC_{50} values, and four compounds (**36**, **41**, **45** and **67**) had IC_{50} values in the 1.0−2.0 μM range.

*3.1.3.1. ARDAPs **34-48**: R_1 substituent at position 3 of the 1-phenyl ring.* The 3-amino derivatives at the 1-phenyl ring **42-48** were generally highly potent inhibitors in both the biochemical and cellular assays, with the exception of **45**, which has a nitro group at position 3 of the 4-phenyl ring. ARDAPs **42**, **44** and **48** were the most potent MCF-7 cancer cell growth inhibitors of this group, with IC_{50} values of 17, 14 and 14 nM, respectively. When the Ring A substituent was a 3-methyl group (**34-40**) or a 3-fluorine atom (**41**), there was a significant reduction in antiproliferative activity, with the exception of **40** (IC_{50} = 18 nM). The derivative with a 2-nitro group on the 4-phenyl ring (**44**, IC_{50} = 14 nM) was a strong inhibitor of the MCF-7 cancer cell growth. The presence of an amino group on Ring B positively affected both the inhibition of tubulin assembly and MCF-7 cancer cell growth, in particular when the amino group was at position 4 of Ring B (compare **40**, IC_{50} of 18 nM. and **48,** IC_{50} of 14 nM).

*3.1.3.2. ARDAPs **49-69**: R_1 substituent at position 4 of the 1-phenyl ring.* With three exceptions, **59**, **60** and **66**, these ARDAPs were potent inhibitors of tubulin polymerization, with IC_{50} values at submicromolar concentrations. The most potent derivatives were characterized by the presence of a 3- or 4-amino group on the 4-phenyl ring (**54**, tubulin assembly IC_{50} = 0.42 μM, MCF-7 IC_{50} = 53 nM; **55**, tubulin assembly IC_{50} = 0.36 μM, MCF-7 IC_{50} = 6.0 nM; **61**, tubulin IC_{50} = 0.41 μM, MCF-7 IC_{50} = 53 nM; **62**, tubulin assembly IC_{50} = 0.50 μM, MCF-7 IC_{50} = 12 nM; **68**,

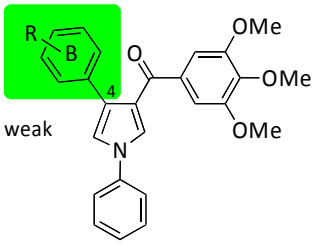
tubulin IC_{50} = 0.87 μM, MCF-7 IC_{50} = 78 nM; **69**, tubulin assembly IC_{50} = 0.38 μM, MCF-7 IC_{50} = 15 nM). The derivatives **49-55**, with a 4-methyl substituent on Ring A, were all potent inhibitors of tubulin assembly, with the Ring B substituents 2-fluoro (**49**), 2-nitro (**51**), 3-amino (**54**) and 4-amino (**55**) also being highly effective inhibitors of MCF-7 cancer cell growth. Among the 4-fluorophenyl derivatives **56-62**, introduction of a nitro group (**59** and **60**) yielded compounds with little ability to inhibit tubulin polymerization and reduced antiproliferative activity. Among this group of compounds, the best antiproliferative activity was observed with **56**, **58** and, especially, **62**, with an IC_{50} of 12 nM against the MCF-7 cells. Generally, ARDAPs **63-69**, bearing a 4-aminophenyl moiety, showed potent inhibition of tubulin assembly and MCF-7 cancer cell growth, with the exception of nitro compounds **66** and **67**. In this group, exceptional antiproliferative and antitubulin activity was observed in compound **69**, with *para*-amino substituents in both Rings A and B. A SAR summary of tubulin polymerization inhibition and inhibition of MCF-7 cancer cell growth of compounds **2-69** is shown in Chart 2.

Chart 2.
SAR Summary for tubulin polymerization inhibition (TPI) and MCF-7 cancer cell growth inhibition (CGI) by compounds **2-69**.



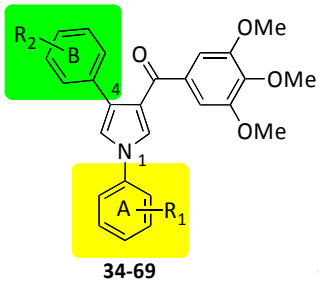
2-16

Ring A
2-subst-Ph: TPI and CGI bad
3-subst-Ph: TPI good, CGI bad
4-subst-Ph: TPI and CGI good



Ring B
TPI: good
CGI: all rings, weak

17-33



34-69

Rings A	Ring B	
3-Me-Ph,	all, except NO_2:	TPI good, CGI weak
3-NH_2-Ph,	all:	TPI good, CGI good
4-Me-Ph,	all:	TPI vey good, CGI good
4-F-Ph,	all, expt NO_2:	TPI very good, CGI good
4-NH_2-Ph,	all, expt NO_2:	TPI and CGI excellent

3.2. Inhibition of the binding of [^{3}H]colchicine to tubulin. Compounds **2-69** were also examined for potential inhibition of the binding of [^{3}H]colchicine to tubulin. ARDAP compounds **12**, **40**, **42-44**, **48**, **49**, **54**, **55**, **62**, **63** and **69** yielded >75% inhibition of the binding reaction. Is should be noted that only one (**12**) among **2-16** with Ring B = phenyl (Table 1) and none of compounds **17-33** with Ring A = phenyl (Table 2) showed binding inhibition >75%. The most potent derivatives **42**, **44**, **48**, **55**, **62** and **69**, Rings A and B = aryl (Table 3), showed good correlation between binding inhibition with a range of 87% (**69**) – 95% (**55**) and inhibition of the MCF-7 cancer cell growth with IC_{50} ≤17 nM. Compounds with 80-90% inhibition of [^{3}H]colchicine binding inhibited the growth of the MCF-7 cancer cell line with IC_{50} values in the range of 12-53 nM; except for **50**, compounds with 70-80% inhibition of [^{3}H]colchicine binding inhibited the growth of the MCF-7 cancer cells with IC_{50}'s in the range of 28-65 nM.

3.3. Inhibition of leukemia KU812, LAMA84-S, LAMA84-R, KBM5-WT, and KBM5-T315I cells.

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of hematopoietic stem/progenitor cells [14]. CML arises from reciprocal chromosome translocation t(9;22)(q34;q11) leading to the Philadelphia (Ph) chromosome encoding for the hybrid phosphoprotein tyrosine kinase P210BCR-ABL that activates downstream signals leading to the pathogenesis of CML [15,16]. CML predominantly affects adults, although it can also occur in young people, accounting for 20% of adult leukemias. The NIH SEER Program has estimated 8990 new cases and 1140 deaths in 2019 in the United States [17].

Imatinib mesylate (IM, STI-571, Gleevec) is a specific BCR-ABL and c-ABL tyrosine kinase inhibitor (TKI), and it represents the standard treatment for CML. Treatment with the drug leads to stable clinical responses and extended overall survival in the majority of patients. However, patients treated with IM develop clinical resistance [18] to the drug due to point mutations in the catalytic domain of the BCR/ABL oncoprotein [19] or to *bcr/abl* gene amplification [20]. Such events usually result in CML patients having a fatal blast crisis. The BCR/ABL threonine for isoleucine mutation at the “gatekeeper” position 315, T315I, causes drug resistance to IM and other tyrosine kinase inhibitors (TKIs) [21,22]. New agents to overcome the IM drug resistance in CML cells are needed. MTs have received attention as a target for the development of alternative therapy for CML [10,11]. Recently, prototypic ARDAP [12] and MPT [23,24] compounds have been reported as potential agents to treat CML. However, this field requires further exploration.

Table 4
Growth inhibition of KU812, LAMA84-S, LAMA84-R, KBM5-WT and KBM5-T315I cell lines by compounds **42**, **44**, **48**, **62**, **69** and reference nilotinib.

Compd	IC_{50} ± SD (nM)[a]				
	KU812	LAMA84-S	LAMA84-R	KBM5-WT	KBM5-T315I
42	14 ± 4	15 ± 1	14 ± 2	18 ± 4	22 ± 2
44	16 ± 2	18 ± 4	20 ± 2	15 ± 3	21 ± 2
48	8 ± 2	10 ± 4	12 ± 4	14 ± 3	16 ± 3
62	18 ± 3	20 ± 2	22 ± 2	25 ± 2	26 ± 3
69	5 ± 2	8 ± 3	10 ± 2	10 ± 3	12 ± 2
NLT[b]	10 ± 2	11 ± 2	126 ± 21	12 ± 5	2421 ± 2

[a] Cytotoxic concentrations for the indicated cell lines. Experiments were performed in triplicate. Incubation time was 48 h.
[b] NLT: Nilotinib.

ARDAPs **42**, **44**, **48**, **62** and **69** were compared with nilotinib (NLT) in the BCR/ABL-expressing KU812 cells and in the LAMA84-S cell line sensitive to IM and its paired IM resistant LAMA84-R. NLT is a second-generation TKI approved for the treatment of IM-resistant CML, and NLT was superior to IM as a first-line treatment in newly diagnosed CML [25,26]. Compounds **42**, **44**, **48**, **62** and **69** inhibited the KU812, LAMA84-S and LAMA84R cell lines at low nanomolar concentrations (Table 4). NLT was comparable to **42**, **44**, **48**, **62** and **69** in the KU812 and LAMA84-S cells but showed weaker inhibition of the LAMA84-R cell line. At such nanomolar concentrations, peripheral blood mononuclear cells (PBMCs) isolated from healthy donors were minimally affected (data not shown). ARDAPs **42**, **44**, **48**, **62** and **69** also inhibited the IM-sensitive KBM5 and IM-resistant KBM5-T315I cells with similar IC_{50} inhibitory concentrations. Most importantly, the activity of these compounds did not appear to be affected by the T315I mutation; in contrast, NLT, showed weak inhibition of this cell line. As an inhibitor of the IM-resistant LAMA84-R and KBM5-T315I cell lines, **69** (IC_{50} of 10 and 12 nM,

respectively) was 12.6 and 201.7 times superior to NLT.

The ability of **69** to potentiate the cytotoxic effects of NLT was assessed in human KBM5 CML cells. KBM5-WT and KBM5-T315I cells were treated for 48 h with 10 nM NLT in the presence or absence of 10 nM **69** and analyzed by the MTT assay. Apoptosis evaluation by flow cytometry (annexin V-stained cells) showed that **69** potentiates NLT-mediated cell death in both KBM5-WT and KBM5-T315I CML cells. The NLT+**69** drug combination was clearly more effective than NLT or **69** alone in increasing the percentage of apoptotic cells from near 50% to 90% (Fig. 1).

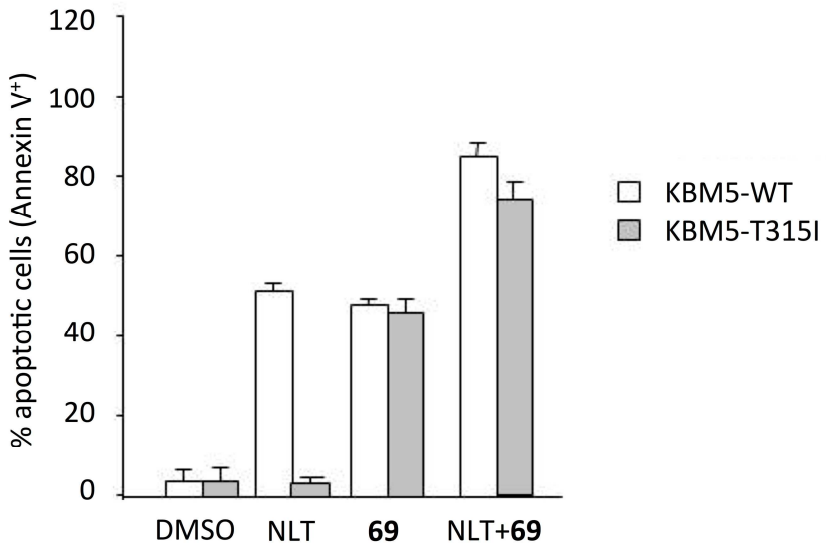


Fig. 1. ARDAP **69** potentiates NLT-mediated CML cell death, including those cells that express the T315I mutation. Cells were treated for 48 h and then assessed by flow cytometric analysis. Experiments were performed in triplicate.

3.4. Inhibition of growth of glioblastoma T98G, U87MG and U343MG and neuroblastoma SK-N-BE and SK-N-BE(2)-C cell lines. Glioblastoma is a highly malignant and rapidly growing type of brain cancer. It is usually aggressive and a relatively common brain tumor in adults [27]. A major difficulty in treating glioblastomas is caused by different cell types found in these tumors. Standard therapy includes surgical resection, followed by postoperative radiation therapy and adjuvant chemotherapy with the alkylating agent temozolomide [28]. Treatments of U343MG (human glioblastoma-astrocytoma), U87MG (human glioblastoma-astrocytoma) and T98G (human glioblastoma) cells with increasing concentrations of compounds **42**, **44**, **48**, **62** and **69** produced a dose-dependent inhibition of cell viability (Fig.s 2SD-4SD, supplementary data). The IC_{50} values obtained were in the nanomolar concentration range in each cell line, and ranged from 12 (**48**) to 69 (**42**) nM in U343MG cells, from 30 (**44**) to 61 (**42**) nM in U87MG cells, and from 22 (**62**) to 54 (**42**) nM in T98G cells.

Neuroblastoma is the most common extracranial solid tumor occurring in children. As inhibitors of the SK-N-BE (human neuroblastoma) and SK-N-BE(2)-C (human neuroblastoma chemio-resistant derived from SK-N-BE) cell lines, compounds **42**, **44**, **48**, **62** and **69** were one order of magnitude less effective than they had been in the glioblastoma cell lines. Compound **48** was the most active in both neuroblastoma cell lines, with EC_{50} values of 221 (SK-N-BE cells) and 56 nM (SK-N-BE(2)-C cells) (Table 5).

Table 5
Growth inhibition of U343G, U87MG, T98G, SK-N-BE and SK-N-BE(2)-C cell lines by compounds **42**, **44**, **48**, **62** and **69.**

Compd	IC_{50} ± SD (nM)[a]				
	U343MG	U87MG	T98G	SK-N-BE	SK-N-BE(2)-C
42	69 ± 5	61 ± 7	54 ± 4	244 ± 1	106 ± 1
44	30 ± 4	30 ± 0.4	35 ± 3	311 ± 1	132 ± 1
48	12 ± 2	31 ± 0.7	37 ± 5	221 ± 1	56 ± 1
62	20 ± 2	46 ± 4	22 ± 3	288 ± 1	178 ± 1
69	22 ± 2	48 ± 5	24 ± 2	303 ± 1	147 ±1

[a] Cytotoxic concentrations for the indicated cell lines. Experiments were performed in triplicate. Incubation time was 48 h. For U343MG cells incubation time was 72 h.

3.5. Inhibition of growth of colorectal HT29, HCT116, SW480 and SW620 cell lines. Colorectal cancer (CRC) is a commonly occurring cancer worldwide, and 95% of these tumors are adenocarcinomas [29]. Early CRC cases are treated by surgery, but often the disease is diagnosed at an advanced stage and sometimes with distant metastases. Adjuvant chemotherapy is needed, but drug resistance may emerge, leading to failure of treatment [30]. Compounds **42**, **44**, **48**, **62** and **69** showed strong inhibition of four CRC cell lines [HT29 (colorectal adenocarcinoma), HCT116 (colorectal carcinoma), SW480 (colorectal adenocarcinoma) SW620 (colorectal adenocarcinoma)] (Table 6). The IC_{50} values obtained ranged from 27 (**48**) in HCT116 cells, to 167 (**62**) nM in SW480 cells. ARDAP **48** was the most potent inhibitor of HCT116, SW480 and SW620 cell lines, whereas **69** was the most active in the HT29 cells.

Table 6
Growth inhibition of HT29, HCT116, SW480, SW620 and T24 cell lines by compounds **42, 44, 48, 62** and **69**

Compd	IC_{50} ± SD (nM)[a]				
	HCT116	HT29	SW480	SW620	T24
42	42 ± 2	56 ± 1	162 ± 1	123 ± 1	34 ± 1
44	44 ± 2	51 ± 2	164 ± 1	38 ± 1	12 ± 2
48	27 ± 2	51 ± 2	48 ± 1	28 ± 1	12 ± 1
62	36 ± 2	35 ± 2	167 ± 4	47 ± 1	48 ± 1
69	41 ± 5	34 ± 1	153 ± 1	61 ± 1	58 ± 1

[a] Cytotoxic concentrations for the indicated cell lines. Experiments were performed in triplicate. Incubation time was 48 h.

3.6. Inhibition of growth of urinary bladder T24 and ovary carcinoma ES-2 Cells. Compounds **42**, **44**, **48**, **62** and **69** inhibited the growth of urinary bladder T24 cancer cells with IC_{50}'s in the nanomolar range ARDAPs **44** and **48** (IC_{50} of 12 nM in both cell lines) showed the strongest antitumor activity (Table 6). The highly potent ARDAP **48** was evaluated as an inhibitor of human ovary carcinoma ES-2 cells. In this assay **48** showed IC_{50} of 118 nM.

3.7. Drug-like properties of compounds **42**, **44**, **48**, **62** and **69** were predicted through the most common descriptors of drug-likeness. The physical and chemical descriptors of the Lipinski [31] Veber [32] and Egan [33] rules were computed to evaluate the bioavailability after oral administration of derivatives **42**, **44**, **48**, **62** and **69**. There was no violation of the rules for these five compounds, so they were predicted to have a good oral bioavailability (Table 7). The data of derivative **48** are summarized in the radial graph (Fig. 2).

Table 7
Physico-chemical profiles of compounds **42**, **44, 48, 62** and **69**.

Comp	Mw[a,b]	H don[a,c]	H acc[a,d]	logP[a,e]	logS[a,f]	tPS[a,g]	Lr[a,h]	Vr[a,i]	Er[a,j]	Caco[k,l]	MDCK[k,m]	Khsa[k,*n*]
42	446.47	2	6	4.62	-5.36	75.7	0	0	0	1276	932	0.99
44	473.48	3	9	4.35	-5.28	121.5	0	0	0	228	100	0.9
48	443.50	4	7	3.84	-4.84	101.7	0	0	0	323	145	0.71
62	446.47	2	6	4.62	-5.36	75.7	0	0	0	1277	1165	0.99
69	443.50	4	7	3.84	-4.84	101,73	0	0	0	323	145	0.71

[a] Physicochemical properties predicted by FAF-drug4 server [34,35].
[b] Molecular weight.
[c] Number of H-bond acceptors.
[d] Number of H-bond donors.
[e] Octanol-water partition coefficient predictor by XLOGP3 method [36].
[f] Logarithm of compound water solubility by ESOL method [37].
[g] Topological polar surface area.
[h] Lr: Lipinsky Rule deviation (log P <5, H-bond donors ≤5, H-bond acceptors ≤10, and a molecular weight <500) [31].
[h] Vr: Veber rule deviation (rotatable bonds ≤10, tPSA ≤140) [32].
[j] Er: good/bad bioavailability (0≥ tPSA ≤132 and -1≥ logP ≤6) [33]
[k] Physicochemical properties predicted by QikProp [38].
[l] Caco: Apparent Caco-2 permeability (nm/sec) (<25 poor, >500 great).
[m] MDCK - Apparent MDCK permeability (nm/sec) (<25 poor, >500 great). [*n*]Logarithm of the predicted binding to human serum albumin (-1.5 – 1.5).

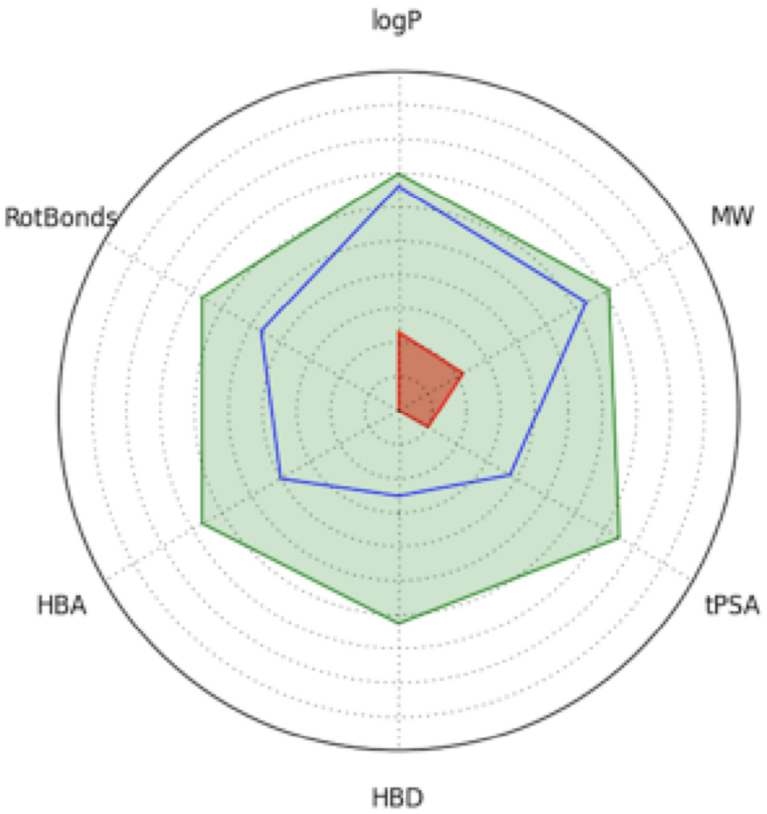


Fig 2. A radial plot representing the computed oral bioavailability profile of **48.** Structural properties of compounds are compared with the optimal blue area defined from Rule-of-five and Veber's rules. Compound values (blue line) should fall within the green area; the red one, being an extreme zone, generally indicates low oral bioavailability. The computations involved logP, molecular weight (MW), topological polar surface area (tPSA), rotatable bonds (RotB), H-bond acceptors and donors (HBA, HBD).

*3.8. Metabolic stability of compound **48**.* Aniline compounds may potentially cause methemoglobin formation and hemolysis as their most prominent adverse effects. In particular, the *N*-hydroxylation of aniline is responsible for oxidation of Fe(II) of oxyhemoglobin to Fe(III). Hemoglobin-Fe(III) is a weak carrier of oxygen to tissues and leads to methemoglobinemia, low levels of oxygen in the blood and red blood cell damage. Oxidation of the amino group of the aniline decreases the amount of hemoglobin binding and increases mutagenicity and carcinogenicity [39]. While several aniline compounds may undergo oxidation, there are also

many examples of drugs with aniline substructures that escape oxidative metabolism. Since the most active derivatives reported in this work share aniline moieties, we evaluated *in silico* the metabolic reactivity of these groups. Using the P450 module from the Schrödinger suite [40], we computed the intrinsic reactivity of all atoms of the derivative **48** to the 3A4 Cyp isoform. The carbon atoms of the methoxy groups and the unsubstituted aromatic carbon atoms of the trimethoxyphenyl moiety showed higher likelihood of reactivity than the aniline nitrogen atoms, which were predicted to have a low likelihood of oxidation. The computational prediction suggests negligible metabolic oxidation of the aniline groups of **48**. Further development of these agents will include aniline group masking by their inclusion in heterocyclic rings or carboxamide groups.

*3.9. In vivo antitumor activity of compound **48.*** Tumors could be observed on the backs of the mice (injected T24 or ES-2) in the saline treatment group on Day 22, whereas no tumors were found on the backs of the **48**-treated nude mouse group. Mice were euthanized on Day 40, and tumors on the backs were collected for measurement of tumor volume and weight. Results showed that the tumors from the group treated with **48** were significantly smaller than those obtained from the control group (saline treatment) in terms of both tumor volume and weight (Fig- 3). Meanwhile, hematoxylin and eosin (HE) staining showed that the type of tumor formed in the two groups were human bladder transitional cell carcinoma (from T24-injected mice) or human ovarian clear cell carcinoma (from ES-2-injected mice) (Figure 5SD, supplementary data).

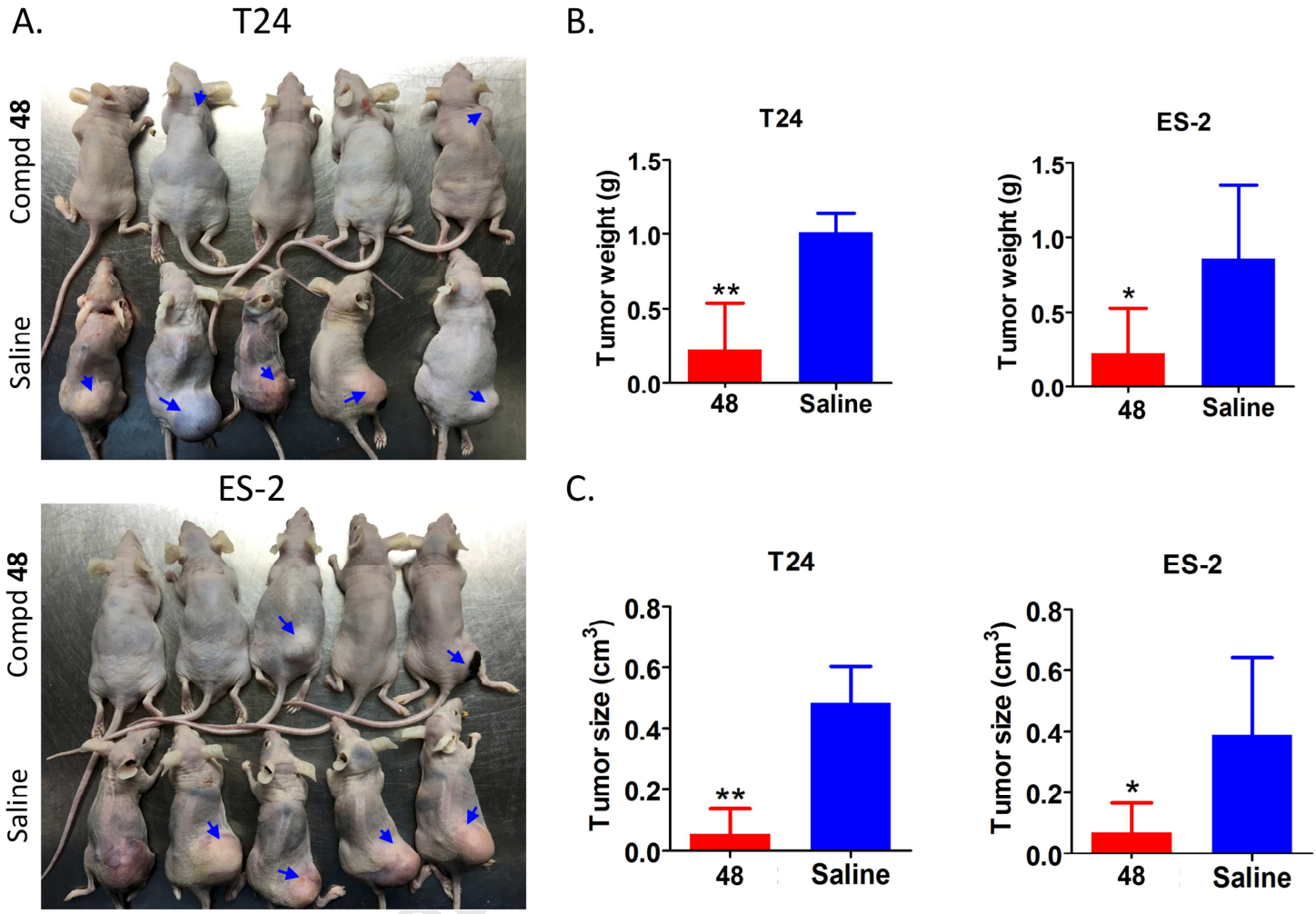


Fig. 3. A. Mice injected with T24 (top panel) or ES-2 (bottom panel) tumors after 40 days of treatment with compound **48** or with saline. B. Tumor weight at day 40. C. Tumor size at day 40.

Immunofluorescence staining results showed that the tumors from the **48**-treated group (ES-2 or T24) had significantly lower expression of the proliferation factor Ki67, a marker for tumor angiogenesis CD31, a mitochondrial stability protein Bcl-2, compared with the control group (Fig. 4). In addition, the tumors from the untreated group (ES-2 or T24) had significantly higher expression of apoptotic factors caspase 9 and caspase 3 and a mitochondrial disintegration

protein Bax, compared with the control group (Fig. 5). Thus, *in vivo* experiments showed that **48** significantly inhibited cancer cell proliferation, *in vivo* tumorigenesis, and tumor angiogenesis.

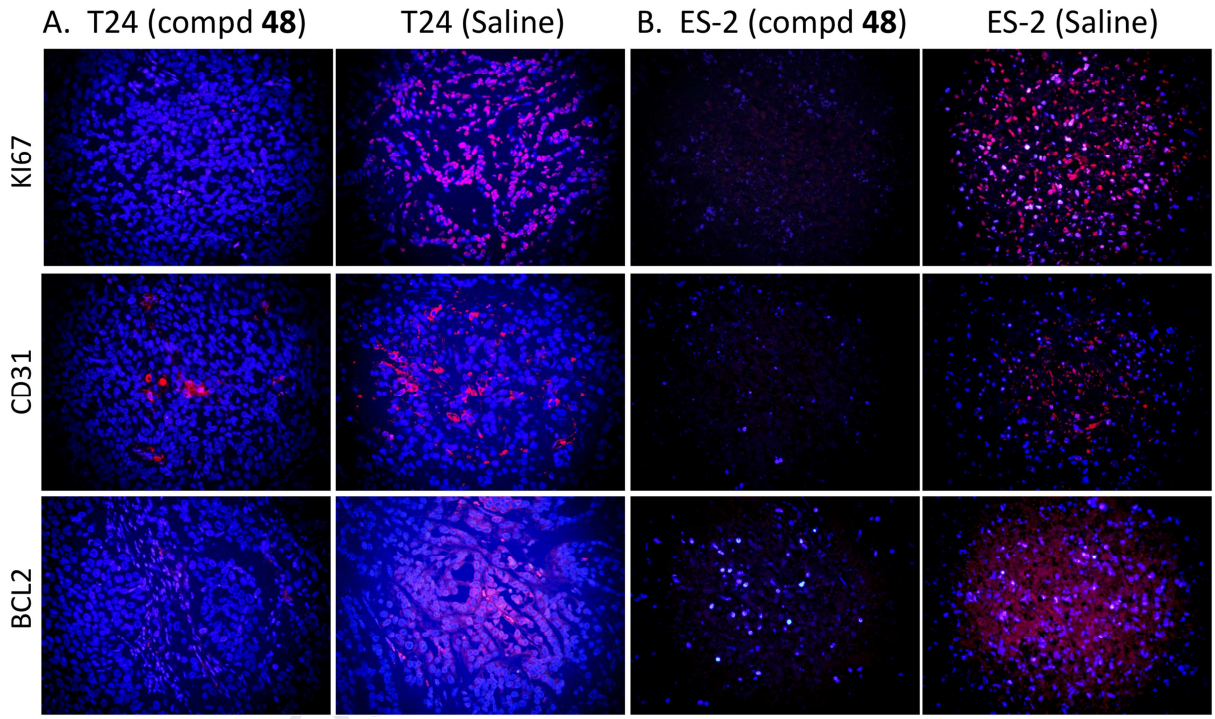


Fig. 4. Immunofluorescence staining results of tumor proliferation and angiogenesis markers. Immunofluorescence staining results showed that the tumors from the **48** treated group have significantly lower expression of the proliferation factor Ki67, a marker for tumour angiogenesis CD31, a mitochondrial stability protein Bcl-2, compared with the control group. Original magnification ×200.

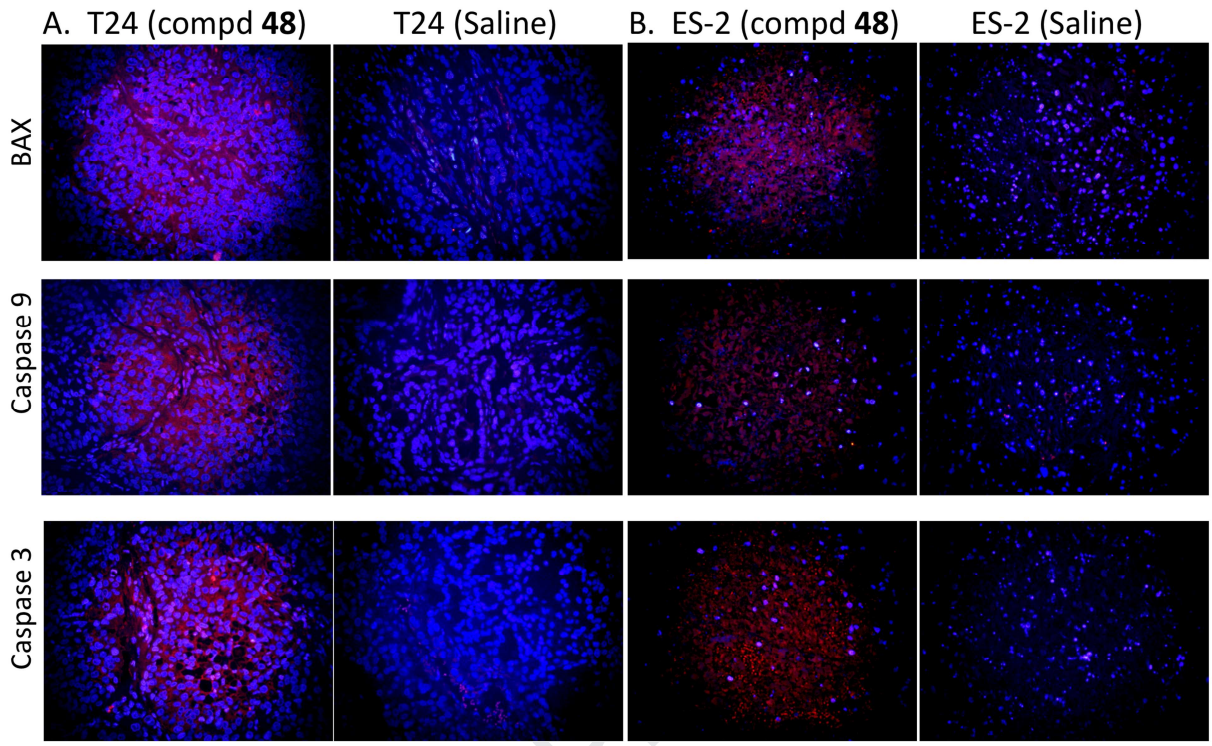


Fig. 5. Immunofluorescence staining results of cellular apoptotic markers. Immunofluorescence staining results showed that the tumours from the **48** treated group have have significantly higher expression of the Apoptotic family factors Caspase 9 and Caspase 3, and a mitochondrial disintegration protein Bax, compared with the control group. Original magnification ×200.

4. Conclusion

We synthesized three series of 3-aroyl-1,4-diarylpyrrole (ARDAP) derivatives, **2-16**, **17-33** and **34-69**, to explore SARs of the phenyl rings at position 1 and 4 of the pyrrole. Among ARDAPs **2-16** bearing a substituted phenyl ring at position 1 of the pyrrole, the 1-(4-bromophenyl) derivative **12** was the most potent inhibitor of tubulin polymerization with an IC_{50} of 0.66 μM and of the growth of the human MCF-7 nonmetastatic breast cancer epithelial cells with an IC_{50} of 20 nM. ARDAPs bearing a substituent at position 4 of the 1-phenyl ring were generally superior to the corresponding 3-substituted counterparts. Introduction of a substituent at position 2 of the 4-phenyl ring of **17-33** provided tubulin polymerization inhibitors with IC_{50}

values at submicromolar concentrations. The most potent MCF-7 cell growth inhibition correlated with the presence of a nitro group at position 2 of the phenyl at position 4 (**24**, IC_{50} of 49 nM). Among ARDAPs bearing substituents at both 1- and 4-phenyl rings, introduction of one or two amino group(s) at position(s) 3,4 of the phenyl rings resulted generally in highly potent inhibitors in both biochemical and cellular assays; **42**, **44**, **48, 54, 62, 68** and **69** were the most potent MCF-7 cell growth inhibitors with nanomolar IC_{50}s. Compounds **42**, **44**, **48**, **62** and **69** inhibited the KU812, LAMA84-S, LAMA84-R, KBM5-WT and KBM5-T315I leukemic cell lines at low nanomolar concentrations and were definitely superior to the reference second generation TKI NLT as inhibitors of the IM-resistant LAMA84-R and KBM5-T315I cells. Intriguingly, ARDAP derivative **69** was uniformly effective as an inhibitor of the CML cell lines independently on the molecular mechanisms underlying TKI resistance. Indeed, LAMA-84R cells express heightened levels of Bcr/Abl protein and mRNA compared to LAMA84 [45], whereas KBM5-T315I cells express a mutation in the drug binding site *vs* KMB5-WT. Our results therefore imply less risk of cross-resistance of **69** with TKI and provide the basis of alternative synergistic targets for combined therapeutic strategies in CML-resistant and -sensitive cells. Accordingly, we observed that the ARDAP derivative **69** enhanced NLT-mediated cell death in both KBM5-WT and KBM5-T315I CML cells, with the NLT+**69** combination superior to NLT or **69** alone in increasing the percentage of cells in apoptosis. Compounds **42**, **44**, **48**, **62** and **69** produced a dose-dependent inhibition of cell viability in glioblastoma T98G, U87MG and U343MG cells, in colorectal HT29, HCT116, SW480 and SW620 cells, and in urinary bladder T24 cells yielding low nanomolar IC_{50} values. In the T24 and ES-2 animal models, compound **48** exhibited significant inhibition of cancer cell proliferation, *in vivo* tumorigenesis, and tumor angiogenesis.

In conclusion, the new 3-aroyl-1,4-diarylpyrroles were potent inhibitors of tubulin polymerization. Compounds **42**, **44**, **48**, **62** and **69** showed strong and broad-spectrum anticancer activity in breast carcinoma, leukemia, glioblastoma, colorectal and urinary bladder cancer cells. Compound **48** was generally more effective as an inhibitor of the glioblastoma, colorectal and urinary bladder cancer cells, whereas **69** consistently was more active as an inhibitor of the CML cell lines. These results highlight that the introduction of amino groups on both the 1- and 4-phenyl rings of the ARDAP scaffold is an effective strategy to obtain new broad-spectrum anticancer agents. Compounds **48** and **69** are robust lead compounds for the design of a new class of anticancer agents active in different types of solid and hematological tumors. These findings prompted the synthesis of new ARDAP analogues. The results will be reported in a forthcoming publication.

5. Experimental protocols

5.1. Chemistry

All reagents and solvents were handled according to the material safety data sheet of the supplier and were used as purchased without further purification. Microwave-assisted reactions were performed on a CEM Discover SP single-mode reactor equipped with an Explorer 72 autosampler, controlling the instrument settings by PC-running CEM Synergy 1.60 software. Closed vessel experiments were carried out in capped microwave-dedicated vials (10 mL) with a cylindrical stirring bar (length 8 mm, diameter 3 mm). Stirring, temperature, irradiation power, maximum pressure (Pmax), pressure set point, times at set point, delta pressure, PowerMAX (simultaneous cooling-while-heating), ActiVent (simultaneous venting-while-heating), and ramp

and hold times were set as indicated. Reaction temperature was monitored by an external CEM fiber optic temperature sensor. After completion of the reaction, the mixture was cooled to 25 °C via air-jet cooling. Organic solutions were dried over anhydrous sodium sulfate. Evaporation of solvents was carried out on a Büchi Rotavapor R-210 equipped with a Büchi V-850 vacuum controller and a Büchi V-700 vacuum pump. Column chromatography was performed on columns packed with silica gel from Merck (70−230 mesh). Silica gel thin layer chromatography (TLC) cards from Merck (silica gel precoated aluminum cards with fluorescent indicator visualizable at 254 nm) were used for TLC. Developed plates were visualized with a Spectroline ENF 260C/FE UV apparatus. Melting points (mp) were determined on a Stuart Scientific SMP1 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrophotometer equipped with a universal attenuated total reflectance accessory. IR data were acquired and processed by PerkinElmer Spectrum 10.03.00.0069 software. Band position and absorption ranges are given in cm^{-1}. Proton (^{1}H NMR) and carbon-13 (^{13}C NMR) nuclear magnetic resonance spectra were recorded with a Varian Mercury (300 MHz) or a Bruker Avance (400 MHz) spectrometer in the indicated solvent, and the corresponding fid files were processed by MestreLab Research SL MestreReNova 6.2.1-769 software. Chemical shifts are expressed in δ units (ppm) from tetramethylsilane. Mass spectra were recorded on a Bruker Daltonics MicroTOF LC/MS mass spectrometer equipped with a positive ion ESI source.

Compound purity. The purity of tested compounds was checked by high pressure liquid chromatography (HPLC). Purity of tested compounds was found to be >95%. Thermo Fisher Scientific Inc. Dionex UltiMate 3000 HPLC system consisted of an SR-3000 solvent rack, a LPG-3400SD quaternary analytical pump, a TCC-3000SD column compartment, a DAD-3000 diode array detector, and an analytical manual injection valve with a 20 μL loop. Samples were

dissolved in acetonitrile (1 mg/mL). HPLC analysis was performed by using a Thermo Fisher Scientific Inc. Acclaim 120 C18 column (5 μm, 4.6 mm × 250 mm), at 25 ± 1 °C with an appropriate solvent gradient (acetonitrile/water), flow rate of 1.0 mL/min and signal detector at 206, 230, 254 and 365 nm. Chromatographic data were acquired and processed by Thermo Fisher Scientific Inc. Chromeleon 6.80 SR15 Build 4656 software.

*5.1.1. General procedure A. Preparation of compounds **2**, **26**, **30** and **33**. Example: (1-(2-Methylphenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**2**)*

A solution of 4-phenyl-1*H*-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**90**) (0.30 g, 0.8 mmol), 2-methylphenylboronic acid (0.20 g, 1.16 mmol), copper(II) acetate (0.15 g, 0.8 mmol) and triethylamine (0.15 mL) in dichloromethane (3.6 mL) was stirred at room temperature for 18 h under an Ar stream. The reaction mixture was diluted with water and extracted with ethyl acetate; the organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 2:1 as eluent) to furnish **2** (yield 33%, 0.04 g), mp 62-65 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.32 (s, 3H), 3.71 (s, 3H), 3.78 (s, 6H), 7.13 (s, 2H), 7.19 (t, *J* = 7 Hz, 1H), 7.25-7.32 (m, 3H), 7.35-7.46 (m, 6H), 7.53 ppm (d, *J* = 2.3 Hz, 1H). IR: ν 1640 and 2932 cm^{-1}. MS (ESI): 428.5 (MH^+). $C_{27}H_{25}NO_4$ (427.49).

*5.1.2. (4-(4-Nitrophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**26**)*

Synthesized according to general procedure A, starting from **100** and 2-methylphenylboronic acid. Yield 72%, mp 115-120 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 3.81 (s, 6H), 7.16 (s, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.67-7.69 (m, 2H), 7.79-7.81 (m, 2H), 8.02 (dd, *J* = 2.4 and 10.9 Hz, 2H), 8.16-8.18 ppm (m, 2H). IR: ν 1579 and 2925 cm^{-1}. MS (ESI): 459.3 (MH^+). $C_{26}H_{22}N_2O_6$ (458.46).

*5..1.3. (4-(5-Bromo-2-methoxyphenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**30**)*

Synthesized according to general procedure A, starting from **104** and 5-bromo-2-methoxyphenylboronic acid. Yield 62%. Mp 148-150 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.38 (s, 3H), 3.66 (s, 3H), 3.72 (s, 6H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.95 (s, 2H), 7.29-7.34 (m, 2H), 7.49-7.53 (m, 3H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.93 ppm (d, *J* = 2.4 Hz, 1H). IR: ν 1581 and 2935 cm^{-1}. MS (ESI): 523.5 (MH^+). $C_{27}H_{24}BrNO_5$ (522.39).

*5.1.4. (1-Phenyl-4-styryl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**33**)*

Synthesized according to general procedure A, starting from **107** and styrylboronic acid. Yield 60%, mp 72-75 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.76 (s, 3H), 3.84 (s, 6H), 7.14 (t, *J* = 7.4 Hz, 3H), 7.23-7.25 (m, 1H), 7.35-7.38 (m, 3H), 7.45-7.59 (m, 5H), 7.77 (d, *J* = 7.8 Hz, 2H), 7.94 (d, *J* = 2.0 Hz, 1H), 8.05-8.06 ppm (m, 1H). IR: ν 1582 and 2941 cm^{-1}. MS (ESI): 440.35 (MH^+). $C_{28}H_{25}NO_4$ (439.50).

*5.1.5. Preparation of Compounds **3**, **7**, **24**, **58**. (1-(2-Chlorophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**3**)*

Synthesized according to general procedure A, starting from **90** and 2-chlorophenylboronic acid, by heating at 40 °C. Yield 4%, mp 112-115 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.79 (s, 6H), 7.15 (s, 2H), 7.20-7.23 (m, 1H), 7.27-7.30 (m, 2H), 7.37-7.40 (m, 3H), 7.50-7.53 (m, 2H), 7.64 (d, *J* = 2.3 Hz, 1H), 7.67-7.72 ppm (m, 2H). IR: ν 1579 and 2926 cm^{-1}. MS (ESI): 448.8 (MH^+). $C_{26}H_{22}ClNO_4$ (447.91).

*5.1.6. (1-(3-Chlorophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**7**)*

Synthesized according to general procedure A, starting from **90** and 3-chlorophenylboronic acid, by heating at 40 °C. Yield 61%, mp 112-115 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.12 (s, 2H), 7.18-7.22 (m, 1H), 7.27-7.30 (m, 2H), 7.38-7.39 (m, 3H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.78-7.85 (m, 2H), 7.98-8.05 ppm (m, 2H). IR: ν 1687 and 2935 cm^{-1}. MS (ESI): 448.9 (MH^+). $C_{26}H_{22}ClNO_4$ (447.91)

*5.1.7. (4-(2-Nitrophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**24**).*

Synthesized according to general procedure A, starting from **98** and phenylboronic acid, by heating at 40 °C. Yield 25%, mp 153-155°C (from *n*-hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 6H), 3.89 (s, 3H), 7.08 (s, 1H), 7.20-7.26 (m, 2H), 7.36-7.58 (m, 9H), 7.99 ppm (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.30, 60.90, 106.73, 120.57, 120.84, 123.70, 124.32, 126.68, 127.32, 127.94, 129.96, 132.38, 132.73, 133.76, 134.62, 135.62, 139.21, 141.36, 149.15, 152.81, 189.78 ppm. IR: ν 1523 and 2943 cm^{-1}. MS (ESI): 459.5 (MH^+). $C_{26}H_{22}N_2O_6$ (458,46).

*5.1.8. (1-(4-Fluorophenyl)-4-(2-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**58**)*

Synthesized according to general procedure A, starting from **98** and 4-fluorophenylboronic acid, by heating at 40 °C. Yield 46%, mp 208-210 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86-3.89 (m, 9H), 7.07 (s, 2H), 7.17-7.21 (m, 3H), 7.41-7.49 (m, 5H), 7.53-7.58 (m, 1H), 7.98 ppm (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.33, 60.90, 106.78, 116.69, 117.00, 120.82, 122.78, 122.89, 123.84, 124.33, 126.83, 128.01, 129.66, 132.37, 132.72, 134.55, 135.60, 141.46, 149.16, 12.84, 189.72 ppm. IR: ν 1512 and 2944 cm^{-1}. MS (ESI): 477.3 (MH^+). $C_{26}H_{21}FN_2O_6$ (476.45).

*5.1.9. Preparation of compounds **17-23**, **25**, **27-29**, **31**, **32**, **34-38**, **41**, **49-53**, **56**, **57**, **59** and **60**.*

*(1-Phenyl-4-(2-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**17**)*

Synthesized according to general procedure A, starting from **91** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 7%, mp 120-122 °C (from *n*-hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H), 3.83 (s, 6H), 3.87 (s, 3H), 7.08-7.09 (m, 6H), 7.15-7.16 (m, 1H), 7.25-7.26 (m, 1H), 7.47-7.48 (m, 4H), 7.62 ppm (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.60, 56.23, 60.84, 76.75, 77.07, 77.39, 107.00, 120.30, 120.70, 124.92, 125,40, 125.68, 126.98, 127.16, 127.73, 129.91, 130.31, 134.39, 134.58, 136.47, 139.54, 141.42, 152.66, 190.06 ppm. IR: ν 1638 and 3133 cm^{-1}. MS (ESI): 456.5 (MH^+). $C_{28}H_{25}NO_5$ (455.50).

*5.1.10. (4-(2-Chlorophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**18**)*

Synthesized according to general procedure A, starting from **92** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 30%, mp 155-157 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 6H), 3.86 (s, 3H), 7.09 (s, 1H), 7.16-7.26 (m, 3H), 7.31-7.38 (m, 3H), 7.46-7.50 (m, 5H), 7.61 ppm (d, J = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.23, 60.84, 107.00, 120.82, 121.01, 124.98, 125.04, 125.41, 126.45, 127.11, 128.18, 129.56, 129.90, 131.71, 133.22, 33.59, 134.36, 139.44, 141.39, 152.64, 190.10 ppm. IR: ν 1643 and 2943 cm^{-1}. MS (ESI): 448.9 (MH^+). $C_{26}H_{22}ClNO_4$ (447.91).

*5.1.11. (4-(3-Chlorophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**19**)*

Synthesized according to general procedure A, starting from **93** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 21%, mp 137-139 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H), 3.88 (s, 3H), 7.09 (s, 2H), 7.17-7.26 (m, 5H), 7.34-7.59 ppm (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.23, 60.87, 107.20, 110.02, 120.03, 120.88, 123.73,

126.58, 126.76, 126.83, 127.30, 128.49, 129.28, 129.95, 133.89, 134.40, 136.19, 139.33, 141.68, 152.76, 190.22 ppm. IR: ν 1637 and 2949 cm^{-1}. MS (ESI): 448.8 (MH^+). $C_{26}H_{22}ClNO_4$ (447.91).

*5.1.12. (4-(4-Chlorophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**20**)*

Synthesized according to general procedure A, starting from **94** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 13%, mp 144-146 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 6H), 3.89 (s, 3H), 7.12 (s, 2H), 7.21-7.23 (m, 2H), 7.32-7.36 (m, 3H), 7.44-7.49 (m, 5H), 7.56 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.27, 60.97, 107.26, 119.94, 20.87, 123.54, 126.84, 127.26, 127.50, 128.25, 129.78, 129.94, 132.49, 132.82, 134.39, 139.35, 141.77, 152.78, 190.13 ppm. IR: ν 1636 and 2973 cm^{-1}. MS (ESI):

*5.1.13. (4-(2-Bromophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**21**)*

Synthesized according to general procedure A, starting from **95** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 15%, mp 164-166 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3H), 3.86 (s, 6H), 7.09 (s, 3H), 7.22-7.34 (m, 4H), 7.48-7.60 ppm (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.27, 60.84, 107.03, 120.79, 120.96, 123.92, 124.91, 125.34, 126.88, 127.02, 127.09, 128.38, 129.90, 131.80, 132.75, 134.435, 135.64, 139.44, 141.37, 152.66, 190.00 ppm. IR: ν 1641 and 3135 cm^{-1}. MS (ESI): 493.3 (MH^+). $C_{26}H_{22}BrNO_4$ (492.36).

*5.1.14. (4-(3-Bromophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**22**)*

Synthesized according to general procedure A, starting from **96** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 25%, mp 124-126 °C (from ethanol). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.74 (s, 3H), 3.80 (s, 6H), 7.12 (s, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.34-7.41 (m, 3H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.61 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.87 (s, 1H), 7.99-

8.00 ppm (m, 1H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.79, 59.94, 106.78, 120.08, 120.87, 121.13, 122.57, 125.73, 126.65, 126.78, 127.22, 128.73, 129.66, 129.84, 130.65, 133.93, 136.72, 136.72, 138.53, 140.90, 152.39, 188.91 ppm. IR: ν 1638 and 2930 cm^{-1}. MS (ESI): 493.2 (MH^+). $C_{26}H_{22}BrNO_4$ (492.36).

*5.1.15. (4-(4-Bromophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**23**)*

Synthesized according to general procedure A, starting from **97** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 7%, mp 149-151 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83 (s, 6H), 3.89 (s, 3H), 7.12 (s, 2H), 7.21-7.26 (m, 2H), 7.36-7.56 ppm (m, 9H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.26, 60.97, 107.22, 119.92, 120.59, 120.85, 123.45, 126.89, 127.26, 127.47, 129.93, 130.11, 131.17, 131.51, 133.26, 134.35, 139.30, 152.75, 190.12 ppm. IR: ν 1634 and 2931 cm^{-1}.

*5.1.16. (4-(3-Nitrophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**25**)*

Synthesized according to general procedure A, starting from **99** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 26% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 6H), 3.89 (s, 3H), 7.13 (s, 2H), 7.32-7.55 (m, 7H), 7.60 (d, J = 2.4 Hz, 1H), 7.76-7.79 (m, 1H), 8.06-8.09 (m, 1H), 8.28 ppm (t, J = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.30, 60.92, 107.10, 120.79, 121.00, 121.41, 123.22, 123.42, 126.49, 127.44, 127.58, 128.87, 130.04, 134.43, 134.80, 136.12, 139.15, 141.80, 148.09, 152.86, 189.92 ppm. IR: ν 1637 and 2937 cm^{-1}. MS (ESI): 459.5 (MH^+). $C_{26}H_{22}N_2O_6$ (458.46).

*5.1.17. 3-(2-Methoxyphenyl)-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1H-pyrrole (**27**)*

Synthesized according to general procedure A, starting from **101** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 6%, mp 142-145 °C (from *n*-hexane). ^{1}H NMR

($CDCl_3$, 300 MHz): δ 3.51 (s, 3H), 3.75 (s, 6H), 3.83 (s, 3H), 6.65 (d, *J* = 9.9 Hz, 1H), 6.92 (t, *J* = 5.4 Hz, 1H), 7.08 (s, 2H), 7.14-7.20 (m, 2H), 7.31-7.37 (m, 2H), 7.46-7.47 (m, 4H), 7.62 ppm (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 54.72, 56.14, 60.82, 106.84, 110.39, 119.71, 120.55, 120.68, 123.76, 124.80, 125.27, 126.77, 128.43, 129.82, 133.95, 139.65, 141.21, 152.41, 155.92, 190.60 ppm. IR: ν 1635 and 2930 cm^{-1}. MS (ESI): 444.5 (MH^+). $C_{27}H_{25}NO_5$ (443.49).

*5.1.18. (4-(3-Methoxyphenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**28**)*

Synthesized according to general procedure A, starting from **102** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 10% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.72 (s, 3H), 3.80 (s, 6H), 3.86 (s, 3H), 6.73-6.76 (m, 1H), 6.88-6.89 (m, 1H), 6.95-6.97 (m, 1H), 7.11 (s, 2H), 7.15-7.24 (m, 2H), 7.34-7.38 (m, 1H), 7.46-7.50 (m, 4H), 7.60 ppm (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 55.15, 56.20, 60.87, 107.32, 112.39, 114.26, 119.64, 120.81, 121.00, 123,96, 126.40, 127.10, 128.35, 129.11, 129.90, 134.32, 135.69, 139.46, 141.59, 152.64, 159.36, 190.46 ppm. IR: ν 1637 and 2937 cm^{-1}. MS (ESI): 444.3 (MH^+). Calcd. for $C_{27}H_{25}NO_5$ (443.49).

*5.1.19. (4-(4-Methoxyphenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**29**)*

Synthesized according to general procedure A, starting from **103** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 94%, mp 67-69 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.78-3.88 (m, 12H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.13-7.18 (m, 3H), 7.30-7.56 ppm (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 55.24, 56.21, 60.91, 107.26, 109.99, 113.62, 119.25, 120.74, 123.59, 126.49, 126.75, 127.00, 128.26, 129.64, 129,87, 133,82, 134.44, 139.48, 141.48, 152.64, 158.48, 190.50 ppm. IR: ν 1635 and 2939 cm^{-1}. MS (ESI): 444.4 (MH^+). $C_{27}H_{25}NO_5$ (443.49).

*5.1.20. (4-(2,5-Difluorophenyl)-1-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**31**)*

Synthesized according to general procedure A, starting from **105** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 7% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.80 (s, 6H), 7.10 (s, 2H), 7.11-7.17 (m, 2H), 7.30-7.38 (m, 2H), 7.52 (t, J = 9 Hz, 2H), 7.76-7.80 (m, 3H), 8.02 ppm (d, *J* = 2.4 Hz, 1H). IR: ν 1638 and 2943 cm^{-1}. MS (ESI): 450.5 (MH^+). $C_{26}H_{21}F_2NO_4$ (449.45).

*5.1.21. (1-Phenyl-4-(2,4,6-trifluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**32**)*

Synthesized according to general procedure A, starting from **106** and phenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 5%, M.p. 162-164 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 6H), 3.89 (s, 3H), 6.66 (t, J = 8.4 Hz, 2H), 7.11 (s, 2H), 7.26-7.27 (m, 1H), 7.37-7.51 (m, 5H), 7.61 ppm (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.25, 60.90, 99.71, 99.74, 99.97, 100.05, 100.08, 100.122, 100.43, 100.46, 106.79, 112.80, 121.03, 122.25, 124.65, 126.02, 127.38, 129.95, 134.38, 139.34, 141.52, 152.80, 189.78 ppm. IR: ν 1640 and 2942 cm^{-1}. MS (ESI): 468.4 (MH^+). $C_{26}H_{20}F_3NO_4$ (467.44).

*5.1.22. (4-(2-Fluorophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**34**)*

Synthesized according to general procedure A, starting from **108** and 3-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 31%, mp 124-126 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3H), 3.83 (s, 6H), 3.87 (s, 3H), 6.98-7.09 (m, 2H), 7.12 (s, 2H), 7.16-7.21 (m, 2H), 7.27 (d, *J* = 6.0 Hz, 3H), 7.31-7.39 (m, 2H), 7.59 ppm (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.47, 56.20, 60.86, 107.07, 115.29, 115.59, 118.00,

120.99, 121.17, 121.62, 122.34, 122.53, 123.77, 124.40, 125.98, 127.93, 128.35, 128.46, 129.68, 130.99, 131.04, 134.36, 139.43, 140.05, 152.67, 157.99, 161.26, 190.19 ppm. IR: ν 1572 and 3146 cm^{-1}. MS (ESI): 446.4 (MH^+). $C_{27}H_{24}FNO_4$ (445.48).

*5.1.23. (4-(2-Chlorophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**35**)*

Synthesized according to general procedure A, starting from **92** and 3-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 8%, mp 179-181 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3H), 3.84-3.86 (m, 9H), 7.09 (s, 2H), 7.14-7.17 (m, 3H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.26-7.38 (m, 5H), 7.60 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 21.48, 56.23, 60.82, 107.10, 117.98, 121.12, 121.61, 124.97, 125.51, 126.44, 127.90, 128.15, 129.59, 129.71, 131.78, 133.30, 133.74, 134.48, 139.50, 140.04, 141.47, 152.70, 190.13 ppm. IR: ν 1642 and 3126 cm^{-1}. MS (ESI): 461.9 (MH^+). $C_{27}H_{24}ClNO_4$ (461.94).

*5.1.24. (4-(2-nitrophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**36**)*

Synthesized according to general procedure A, starting from **98** and 3-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 20% as an oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3H), 3.86-3.89 (m, 9H), 7.09 (s, 2H), 7.16-7.26 (m, 4H), 7.34-7.48 (m, 3H), 7.53-7.58 (m, 2H), 7.99 ppm (d, *J* = 9.6, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 21.47, 56.28, 60.88, 106.76, 117.98, 120.65, 121.61, 123.61, 124.21, 124.33, 126,75, 127.89, 128.10, 129.75, 129.94, 132.34, 132.77, 134.72, 139.25, 140.12, 141.37, 149.21, 152.85, 189.78 ppm. IR: ν 1638 and 2938 cm^{-1}. MS (ESI): 473.4 (MH^+). $C_{27}H_{24}N_2O_6$ (472.49).

*5.1.25. (4-(3-Nitrophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**37**)*

Synthesized according to general procedure A, starting from **99** and 3-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 47%, mp 57-59 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (s, 3H), 3.85-3.89 (m, 9H), 7.12 (s, 2H), 7.19-7.48 (m, 6H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.76-7.78 (m, 1H), 8.06-8.09 (m, 1H), 8.28-8.29 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 21.47, 56.34, 60.92, 107.23, 118.09, 120.86, 121.37, 121.73, 123.23, 123.32, 126.36, 127.50, 128.35, 128.84, 129.82, 134.49, 134.81, 136.22, 139.16, 140.26, 141.89, 148,14, 152.89, 189.96 ppm. IR: ν 1580 and 2937 cm^{-1}. MS (ESI): 473.5 (MH^+). $C_{27}H_{24}N_2O_6$ (472,49).

*5.1.26. (4-(4-Nitrophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**38**)*

Synthesized according to general procedure A, starting from **100** and 3-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 23%, mp 156-159 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.45 (s, 3H), 3.87-3.91 (m, 9H), 7.17 (s, 2H), 7.20-7.42 (m, 5H), 7.55-7.60 (m, 3H), 8.14 ppm (d, *J* = 9 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 21.47, 56.34, 60.97, 107.25, 118.09, 121.36, 121.71, 123.35, 123.44, 125.04, 126.41, 127.76, 128.42, 128.92, 129.83, 134.28, 139.03, 140.26, 141.40, 142.03, 146.27, 152.92, 189.78 ppm. IR: ν 1582 and 2934 cm^{-1}. MS (ESI): 473.6 (MH^+). $C_{27}H_{24}N_2O_6$ (472.49).

*5.1.27. (1-(3-Fluorophenyl)-4-(2-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**41**)*

Synthesized according to general procedure A, starting from **98** and 3-fluorophenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 9% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz):

δ 3.87-3.90 (m, 9H), 7.05-7.10 (m, 3H), 7.16-7.27 (m, 3H), 7.43-7.61 (m, 5H), 8.00-8.03 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.31, 60.90, 106.74, 108.23, 108.56, 114.02, 114.30, 116.21, 116.25, 120.31, 124.16, 124.39, 124.77, 126.29, 128.12, 129.58, 131.34, 131.47, 132.46, 132.69, 134.43, 152.86, 189.63 ppm. IR: ν 1610 and 2937 cm^{-1}. MS (ESI): 477.3 (MH^+). $C_{26}H_{21}FN_2O_6$ (476.45).

*5.1.28. (4-(2-Fluorophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**49**)*

Synthesized according to general procedure A, starting from **108** and 4-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 15%, mp 150-153 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H), 3.82-3.87 (m, 9H), 6.97-7.09 (m, 3H), 7.12 (s, 2H), 7.16-7.32 (m, 3H), 7.34 (s, 2H), 7.36-7.37 (m, 1H), 7.56 ppm (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.94, 56.20, 60.85, 107.09, 115.28, 115.58, 121.00, 121.04, 121.09, 122.38, 122.57, 123.77, 124.29, 126.02, 128.33, 128.44, 130.39, 131.00, 131.05, 134.39, 137.13, 141.48, 152.66, 158.00, 161.26, 190.18 ppm. IR: ν 1581 and 3146 cm^{-1}. MS (ESI): 446.5 (MH^+). $C_{27}H_{24}FNO_4$ (445.48).

*5.1.28. (4-(2-Chlorophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**50**)*

Synthesized according to general procedure A, starting from **92** and 4-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 9%, mp 174-176 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 3.83-3.85 (m, 9H), 7.09 (s, 2H), 7.13-7.18 (m, 4H), 7.25-7.37(m, 5H), 7.58 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.03, 60.62, 106.94, 120.68, 120.99, 124.71, 124.79, 125.37, 16.28, 127.96, 129.45, 130.26, 131.66, 133.18,

133.65, 134.37, 136.87, 137.11, 141.32, 152.58, 189.93 ppm. IR: ν 1638 and 3132 cm^{-1}. MS (ESI): 462.8 (MH^+). $C_{27}H_{24}ClNO_4$ (461.94).

*5.1.29. (4-(2-Nitrophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**51**)*

Synthesized according to general procedure A, starting from **98** and 4-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 5%, mp 191-193 °C (from ethanol). ^1H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.86-3.89 (m, 9H), 7.08 (s, 2H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.26-7.35 (m, 4H), 7.41-7.59 (m, 4H), 7.99 ppm (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.96, 56.30, 60.90, 106.72, 110.00, 120.67, 120.78, 123.45, 124.06, 124.30, 126.77, 127.86, 129.92, 130.44, 132.33, 132.75, 134.71, 136.90, 137.32, 141.32, 149.19, 152.8, 189.74 ppm. IR: ν 1518 and 2939 cm^{-1}. MS (ESI): 473.5 (MH^+). $C_{27}H_{24}N_2O_6$ (472.49).

*5.1.30. (4-(3-Nitrophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**52**)*

Synthesized according to general procedure A, starting from **99** and 4-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 10%, mp 129-132 °C (from ethanol). ^1H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 3.85-3.88 (m, 9H), 7.12 (s, 2H), 7.26-7.47 (m, 6H), 7.56 (d, *J* = 3.2 Hz, 1H), 7.77 (d, *J* = 10.4 Hz, 1H), 8.06-8.09 (m, 1H), 8.27-8.28 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 20.97, 56.31, 60.91, 107.17, 110.03, 120.93, 121.35, 123.24, 126.30, 127,54, 128.83, 130.52, 134.52, 134.81, 136.25, 136.85, 137.63, 141.82, 148.12, 152.88, 189.91 ppm. IR: ν 1516 and 2937 cm^{-1}. MS (ESI): 473.4 (MH^+). $C_{27}H_{24}N_2O_6$ (472.49).

*5.1.31. (4-(4-Nitrophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**53**)*

Synthesized according to general procedure A, starting from **100** and 4-methylphenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 20%, mp 202-205 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.85-3.89 (m, 9H), 7.17 (s, 2H), 7.27-7.36 (m, 5H), 7.53-7.58 (m, 3H), 8.11 ppm (d, *J* = 12 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 20.97, 56.32, 60.92, 107.35, 120.98, 121.42, 123.36, 123.45, 126.47, 127.85, 128.98, 130.57, 134.40, 136.85, 137.71, 141.49, 142.16, 146.337, 153.02, 189.73 ppm. IR: ν 1580 and 2930 cm^{-1}. MS (ESI): 473.5 (MH^+). $C_{27}H_{24}N_2O_6$ (472.49).

*5.1.32. (4-(2-Fluorophenyl)-1-(4-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**56**)*

Synthesized according to general procedure A, starting from **108** and 4-fluorophenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 15%, mp 144-146 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82 (s, 3H), 3.86 (s, 6H), 6.97-7.08 (m, 2H), 7.11 (s, 2H), 7.16-7.23 (m, 4H), 7.27-7.35 (m, 1H), 7.43-7.47 (m, 2H), 7.53 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.23, 60.86, 107.13, 115.33, 115.63, 116.63, 116.93, 121.16, 121.35, 122.79, 122.90, 123.87, 124.69, 126.06, 128.48, 128.59, 130.98, 131.03, 134.19, 135.81, 141.63, 152.69, 157.97, 159.85, 161.24, 163.13, 190.15 ppm. IR: ν 1579 and 3337 cm^{-1}. MS (ESI): 450.5 (MH^+). $C_{26}H_{21}F_2NO_4$ (449.45).

*5.1.33. (4-(2-Chlorophenyl)-1-(4-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**57**)*

Synthesized according to general procedure A, starting from **92** and 4-fluorophenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 9%, mp 162-165 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84-3.86 (m, 9H), 7.07 (s, 2H), 7.16-7.22 (m, 5H), 7.29-7.36 (m, 2H), 7.43-7.47 (m, 2H), 7.54 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.25,

60.84, 107.05, 116.62. 116.93, 121.27, 122.71, 122.82, 125.07, 125.61, 126.48, 128.25, 129.60, 131.72, 133.19, 133.44, 134.26, 135.79, 135.83, 141.48, 152.66, 159.81, 163.09, 190.13 ppm. IR: ν 1636 and 2959 cm^{-1}. MS (ESI): 466.7 (MH^+). $C_{26}H_{21}ClFNO_4$ (465.90).

*5.1.34. (1-(4-Fluorophenyl)-4-(3-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**59**)*

Synthesized according to general procedure A, starting from **99** and 4-fluorophenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 59%, mp 60-63 °C (from ethanol). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.84-3.88 (m, 9H), 7.11 (s, 2H), 7.18-7.26 (m, 3H), 7.41-7.48 (m, 3H), 7.52-7.53 (m, 1H), 7.74-7.76 (m, 1H), 8.04-8.06 (m, 1H), 8.26-8.26 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.35, 60.90, 107.28, 116.77, 117.08, 121.03, 121.42, 122.94, 123.05, 123.24, 123.59, 126.53, 127.55, 128.88, 134.35, 134.76, 135.56, 136.05, 142.02, 148.12, 152.61, 160.06, 163.35, 189.84 ppm. IR: ν 1512 and 2937 cm^{-1}. MS (ESI): 477.4 (MH^+). $C_{26}H_{21}FN_2O_6$ (476.45).

*5.1.35. (1-(4-Fluorophenyl)-4-(4-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**60**)*

Synthesized according to general procedure A, starting from **100** and 4-fluorophenylboronic acid, by heating at 50 °C in 1,2-dichloroethane. Yield 71%, mp 196-199 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 6H), 3.90 (s, 3H), 7.15 (s, 2H), 7.19-7.28 (m, 3H), 7.43-7.47 (m, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 8.15 ppm (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.36, 60.98, 107.27, 110.02, 116.82, 117.12, 121.46, 122.97, 123.09, 123.49, 123.64, 126.64, 127.79, 128.94, 134.12, 135.40, 135.45, 141.16, 142.16, 146.37, 152.94, 160.09, 163.38, 189.70 ppm. IR: ν 1638 and 2950 cm^{-1}. MS (ESI): 477.5 (MH^+). $C_{26}H_{21}FN_2O_6$ (476.45).

*5.1.36. Preparation of compounds **8**, **10-12** and **15**. (1-(3-Bromophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**8**)*

Synthesized according to general procedure A, starting from **90** and 3-bromophenylboronic acid, by heating at 80 °C in 1,2-dichloroethane. Yield 5% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.77 (s, 6H), 7.12 (s, 2H), 7.18-7.22 (m, 1H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.37-7.39 (m, 2H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.51-7.53 (m, 1H), 7.81-7.83 (m, 2H), 8.04 (d, *J* = 2.2 Hz, 1H), 8.09-8.11 ppm (m, 1H). IR: ν 1579 and 2923 cm^{-1}. MS (ESI): 493.4 (MH^+). $C_{26}H_{22}BrNO_4$ (492.36).

*5.1.37. (1-(3-Methoxyphenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**10**)*

Synthesized according to general procedure A, starting from **90** and 3-methoxyphenylboronic acid, by heating at 80 °C in 1,2-dichloroethane. Yield 5%, mp 68-70 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70 (s, 3H), 3.75 (s, 6H), 3.83 (s, 3H), 6.88-6.91 (m, 1H), 7.10 (s, 2H), 7.18-7.29 (m, 3H), 7.32-7.35 (m, 5H), 7.74-7.75 (m, 1H), 7.96-7.97 ppm (m, 1H). IR: ν 1579 and 2924 cm^{-1}. MS (ESI): 444.3 (MH^+). $C_{27}H_{25}NO_5$ (443,49).

*5.1.38. (1-(4-Chlorophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**11**)*

Synthesized according to general procedure A, starting from **90** and 4-chlorophenylboronic acid, by heating at 80 °C in 1,2-dichloroethane. Yield 8%, mp 162-165 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.77 (s, 6H), 7.11 (s, 2H), 7.18-7.22 (m, 1H), 7.28 (t, *J* = 6.9 Hz, 2H), 7.36-7.38 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.97 ppm (d, *J* = 2.5 Hz, 1H). IR: ν 1574 and 2937 cm^{-1}. MS (ESI): 448.7 (MH^+). $C_{26}H_{22}ClNO_4$ (447.91).

*5.1.38. (1-(4-Bromophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**12**)*

Synthesized according to general procedure A, starting from **90** and 4-bromophenylboronic acid, by heating at 80 °C in 1,2-dichloroethane. Yield 7%, mp 128-130 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70 (s, 3H), 3.76 (s, 6H), 7.10 (s, 2H), 7.18-7.29 (m, 3H), 7.35-7.37 (m, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.74-7.75 (m, 3H), 7.96-7.97 ppm (m, 1H). IR: ν 1573 and 2923 cm^{-1}. MS (ESI): 492.2 (MH^+). $C_{26}H_{22}BrNO_4$ (492.36).

*5.1.39. (1-(4-Methoxyphenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**15**)*

Synthesized according to general procedure A, starting from **90** and 4-methoxyphenylboronic acid, by heating at 80 °C in 1,2-dichloroethane. Yield 5% as an oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70 (s, 3H), 3.75 (s, 6H), 3.78 (s, 3H), 7.02-7.09 (m, 4H), 7.17-7.28 (m, 3H), 7.35-7.37 (m, 2H), 7.62-7.69 (m, 3H), 7.82-7.83 ppm (m, 1H). IR: ν 1583 and 2925 cm^{-1}. MS (ESI): 444.3 (MH^+). $C_{27}H_{25}NO_5$ (443,49).

*5.1.40. (1-(2-Methoxyphenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**6**)*

Synthesized according to general procedure A, starting from **90**, 2-methoxyphenylboronic acid and pyridine at room temperature in dichloromethane. Yield 16% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.70 (s, 3H), 3.77 (s, 6H), 3.84 (s, 3H), 7.05-7.07 (m, 1H), 7.10 (s, 2H), 7.16-7.19 (m, 1H), 7.26 (t, J = 7.4 Hz, 3H), 7.33-7.39 (m, 4H), 7.50-7.52 (m, 1H), 7.58 ppm (d, J = 2.2 Hz, 1H). IR: ν 1581 and 2932 cm^{-1}. MS (ESI): 444.2 (MH^+). $C_{27}H_{25}NO_5$ (443.49).

*5.1.41. General procedure B. Preparation of compounds **4**, **9** and **13**. Example: (1-(2-Nitrophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone* (**4**)

In a flask charged with copper(I) bromide (1.4 mg, 0.01 mmol), 8-quinolinol *N*-oxide (3 mg, 0.02 mmol), and cesium carbonate (640 mg, 1.97 mmol) was added **90** (0.50 g, 1.48 mmol), 1-iodo-2-nitrobenzene (0.25 g, 0.99 mmol) and dimethyl sulfoxide (1.0 mL) under an Ar stream.

The reaction mixture was stirred at 65 °C for 18 h. After cooling, water was added and the mixture was extracted with ethyl acetate; the organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 1:1 as eluent) to furnish **4** (9%, 60 mg), mp 152-155 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 3.82 (s, 6H), 7.12 (s, 2H), 7.22-7.23 (m, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.37-7.43 (m, 3H), 7.61-7.62 (m, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.84-7.90 (m, 2H), 8.17 ppm (d, *J* = 7.8 Hz, 1H). IR: ν 1579 and 2937 cm^{-1}. MS (ESI): 459.2 (MH^+). $C_{26}H_{22}N_2O_6$ (458.46).

*5.1.42. (1-(3-Nitrophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**9**)*

Synthesized according to general procedure B, starting from **90** and 1-iodo-3-nitrobenzene. Yield 34%, mp 164-167 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.14 (s, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.1 Hz, 2H), 7.40-7.41 (m, 2H), 7.79 (t, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 8.15-8.18 (m, 2H), 8.28-8.30 (m, 1H), 8.62-8.63 ppm (m, 1H). IR: ν 1638 and 2940 cm^{-1}. MS (ESI): 459.3 (MH^+). $C_{26}H_{22}N_2O_6$ (458.46).

*5.1.43. (1-(4-Nitrophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**13**)*

Synthesized according to general procedure B, starting from **90** and 1-iodo-4-nitrobenzene. Yield 12%, mp 193-195 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.14 (s, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 8.18 (d, *J* = 2.3 Hz, 1H), 8.34 ppm (d, *J* = 9.2 Hz, 2H). IR: ν 1593 and 2939 cm^{-1}. MS (ESI): 459.4 (MH^+). $C_{26}H_{22}N_2O_6$ (458.46).

*5.1.44. General procedure C. Preparation of compounds **42-46** and **62-66**. Example: (1-(3-Aminophenyl)-4-(2-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**42**)*

A mixture of **108** (160 mg, 0.44 mmol), 3-iodoaniline (100 mg, 0.44 mmol), copper(I) iodide (40 mg, 0.22 mmol), cesium carbonate (210 mg, 0.66 mmol) and 1,10-phenanthroline (80 mg, 0.44 mmol) in 1,4-dioxane (2.3 mL) was stirred at 110 °C for 24 h under a nitrogen stream. After cooling, water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 55:45 as eluent) to furnish **42** (Yield 23%, 40 mg), mp 174-177 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): 3.83-3.87 (m, 11H; 9H after treatment with D_2O), 6.30-6.66 (m, 1H), 7.75-7.76 (m, 1H), 6.81-6.84 (m, 1H), 6.97-7.36 (m, 8H), 7.55 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.02, 60.66, 107.01, 110.55, 113.46, 115.09, 115.39, 120.78, 123.61, 124,04, 125.81, 128.13, 128.23, 130.49, 130.80, 130.84, 134.20, 140.32, 147.70, 152.48, 157.80, 161.07, 190.03 ppm.IR: ν 1630 and 3423 cm^{-1}. MS (ESI): 447.3 (MH^+). $C_{26}H_{23}FN_2O_4$ (446.47).

*5.1.45. (1-(3-Aminophenyl)-4-(2-chlorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**43**)*

Synthesized according to general procedure C, starting from **92** and 3-iodoaniline. Yield 65%, mp 173-175 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.82-3.86 (m, 11H; 9H after treatment with D_2O), 6.64 (dd, *J* = 2.0 and 10.8 Hz, 1H), 6.75 (t, *J* = 2.8 Hz, 1H), 6.82 (dd, *J* = 2.0 and 10.8 Hz, 1H), 7.05-7.07 (m, 2H), 7.13-7.35 (m, 6H), 7.56 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.23, 60.84, 107.03, 107.25, 110.74, 113.73, 121.08, 124.63, 124.73, 125.52, 126.42, 128.10, 129.53, 130.67, 131.70, 133.22, 133.68, 134.43, 140.46, 141.37, 147.72, 152.63, 190.18 ppm. IR: ν 1582 and 3342 cm^{-1}. MS (ESI): 463.8 (MH^+). $C_{26}H_{23}ClN_2O_4$ (462.92).

5.1.46. (1-(3-Aminophenyl)-4-(2-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-

*methanone (**44**)*

Synthesized according to general procedure C, starting from **98** and 3-iodoaniline. Yield 77%, mp 200-203 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84-3.96 (m, 11H; 9H after treatment with D_2O), 6.65-6.82 (m, 3H), 7.11 (s, 2H), 7.21-7.27 (m, 2H), 7.41-7.46 (m, 1H), 7.54-7.55 (m, 1H), 7.55-7.56 (m, 1H), 7.76 (d, *J* = 6.9 Hz, 1H), 8.26 ppm (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.32, 60.90, 106.77, 107.53, 111.07, 114.17, 120.62, 123.43, 124.01, 126.77, 127.87, 129.91, 130.76 132.35, 132.74, 134.67, 140.27, 141.37, 149.17, 152.82, 189.84 ppm. IR: ν 1579 and 3341 cm^{-1}. MS (ESI): 474.3 (MH^+). $C_{26}H_{23}N_3O_6$ (473.48).

*5.1.47. (1-(3-Aminophenyl)-4-(3-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**45**)*

Synthesized according to general procedure C, starting from **99** and 3-iodoaniline. Yield 98%, mp 190-192 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 3.80 (s, 6H), 5.38 (s, 2H, disappeared after treatment with D_2O), 6.56-6.58 (d, *J* = 8.1 Hz, 1H), 6.87-6.88 (m, 2H), 7.11-7.17 (m, 3H), 7.61 (7, *J* = 8.0 Hz, 1H), 7.80-7.90 (m, 3H), 8.08-8.10 (m, 1H), 8.25 ppm (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.34, 60.90, 107.19, 107.25, 110.63, 114.00, 120.84, 121.30, 123.10, 123.22, 126.16, 127.54, 128.81, 130.79, 134.53, 134.77, 136.27, 140.19, 141.89, 148.12, 152.88, 189.98 ppm. IR: ν 1575 and 3339 cm^{-1}. MS (ESI): 474.2 (MH^+). $C_{26}H_{23}N_3O_6$ (473.48).

*5.1.48. (1-(3-Aminophenyl)-4-(4-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**46**)*

Synthesized according to general procedure C, starting from **100** and 3-iodoaniline. Yield 27%, mp 215-218 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.75 (s, 3H), 3.83 (s, 6H), 5.42 (s, 2H, disappeared after treatment with D_2O), 6.59 (d, *J* = 7.5 Hz, 1H), 6.86-6.88 (m,

2H), 6.13-6.17 (m, 3H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.83 (d, *J* = 13.5 Hz, 2H), 8.17 ppm (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.94. 60.05, 105.32, 106.89, 107.55, 112.66, 122.11, 122.34, 123.09, 124.96, 127.50, 128.91, 130.12, 133.99, 139.30, 141.13, 141.66, 145.39, 150.04, 152.50, 188.76 ppm. IR: ν 1583 and 3340 cm^{-1}. MS (ESI): 474.3 (MH^+). $C_{26}H_{23}N_3O_6$ (473.48).

*5.1.49. (1-(4-Aminophenyl)-4-(2-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**63**)*

Synthesized according to general procedure C, starting from **108** and 4-iodoaniline. Yield 50%, mp 135-138 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82-3.86 (m, 11H; 9H after treatment with D_2O), 6.74 (d, *J* = 8.7 Hz, 2H), 6.97-7.07 (m, 3H), 7.12-7.26 (m, 5H), 7.30-7.35 (m, 1H), 7.47 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.20, 60.65, 107.10, 115.26, 115.56, 115.63, 120.65, 121.47, 122.60, 122.75, 123.77, 126.46, 128.20, 128.31, 131.10, 134.57, 141.41, 145.91, 152.65, 158.02, 161.28, 190.20 ppm. IR: ν 1624 and 3335 cm^{-1}. MS (ESI): 447.5 (MH^+). $C_{26}H_{23}FN_2O_4$ (446.47).

*5.1.50. (1-(4-Aminophenyl)-4-(2-chlorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**64**)*

Synthesized according to general procedure C, starting from **92** and 4-iodoaniline. Yield 72%, mp 175-179 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.83-3.85 (m, 11H; 9H after treatment with D_2O), 6.74 (d, *J* = 8.4 Hz, 2H), 7.08-7.10 (m, 3H), 7.14-7.16 (m, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.29-7.35 (m, 2H), 7.49 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.22, 60.82, 107.04, 115.75, 121.54, 122.54, 124.23, 124.44, 125.93, 126.40, 128.01, 129.55, 131.21, 131.81, 133.27, 133.90, 134.64, 141.30, 145.72, 152.65, 190.18 ppm. IR: ν 1520 and 3352 cm^{-1}. MS (ESI): 463.7 (MH^+). $C_{26}H_{23}ClN_2O_4$ (462.92).

*5.1.51. (1-(4-Aminophenyl)-4-(2-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**65**)*

Synthesized according to general procedure C, starting from **98** and 4-iodoaniline. Yield 72%, mp 109-112 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85-3.88 (m, 11H; 9H after treatment with D_2O), 6.71 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.38-7.46 (m, 3H), 7.51-7.57 (m, 1H), 7.95-7.98 pm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.27, 60.86, 106.73, 115.62, 121.12, 122.48, 123.56, 124.24, 127.22, 127,72, 130.10, 130.73, 132.29, 132.78, 134.87, 141.23, 149.20, 152.78, 189.78 ppm. IR: ν 1518 and 2936 cm^{-1}. MS (ESI): 474.4 (MH^+). $C_{26}H_{23}N_3O_6$ (473.48).

*5.1.52. (1-(4-Aminophenyl)-4-(3-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**66**)*

Synthesized according to general procedure C, starting from **99** and 4-iodoaniline. Yield 40%, mp 77-80 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85-3.88 (m, 11H; 9H after treatment with D_2O), 6.75 (d, *J* = 8.1 Hz, 2H), 7.08-7.12 (m, 2H), 7.19-7.27 (m, 4H), 7.40-7.47 (m, 2H), 7.75-7.78 (m, 1H), 8.03-8.06 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.33, 60.90, 107.24, 115.65, 121.20, 121.38, 122.66, 122.71, 123.26, 125.86, 128.04, 128.78, 130.68, 134.72, 134.80, 136.46, 141.79, 146.31, 148.12, 152.87, 190.01 ppm. IR: ν 1551 and 2922 cm^{-1}. MS (ESI): 474.2 (MH^+). $C_{26}H_{23}N_3O_6$ (473,48).

*5.1.53. (1-(4-Aminophenyl)-4-(4-nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**67**)*

Synthesized according to general procedure C, starting from **100** and 4-iodoaniline. Yield 64%, mp 228-230 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.74-3.82 (m, 9H), 4.18 (s, 2H, disappeared after treatment with D_2O), 6.68 (d, *J* = 8.7 Hz, 2H), 7.15 (s, 2H), 7.40 (d, *J* =

8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.76 (d, *J* = 1.8 Hz, 2H), 8.15 ppm (d, *J* = 8.7 Hz, 2H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.91, 60.05, 106.89, 114.13, 121.70, 121.81, 122.39, 123.07, 124.61, 127.79, 127.95, 128.87, 134.12, 141.04, 141.95. 145.26, 148.04, 152.48 ppm. IR: ν 1637 and 3389 cm^{-1}. MS (ESI): 474.2 (MH^+). $C_{26}H_{23}N_3O_6$ (473.48).

*5.1.54. (4-Phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**16**)*

Synthesized according to general procedure C, starting from **90** and 5-iodo-1,2,3-trimethoxybenzene in DMF at 110 °C overnight. The crude product was purified by silica gel column chromatography ($CHCl_3$:AcOEt 95:5 as eluent), Yield 19%, mp 80-82 °C (from CH_2Cl_2/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.78 (s, 6H), 3.85 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 6.67 (s, 2H), 7.10 (s, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.20-7.35 (m, 5H), 7.56 ppm (d, *J* = 2.4 Hz, 1H). IR: ν 1636 and 2941 cm^{-1}. MS (ESI): 504.5 (MH^+). $C_{29}H_{29}NO_7$ (503.54).

*5.1.55. General procedure D. Preparation of compounds **5**, **14**, **39**, **47**, **48**, **54**, **55**, **61**, **62**, **68**, **69**. Example: (1-(2-aminophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**5**)*

A mixture of **4** (40 mg, 0.09 mmol) and tin(II) chloride dihydrate (100 mg, 0.44 mmol) and ethyl acetate (1.2 mL) was stirred at 80 °C for 3 h. The mixture was made basic with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 3:7 as eluent) to furnish **5** (47%, 80 mg) as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.71 (s, 3H), 3.79 (s, 6H), 5.22 (s, 2H, disappeared after treatment with D_2O), 6.66 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 7.12 (t, *J* = 7 Hz, 1H), 7.17-7.21 (m, 4H), 7.24-7.30 (m, 3H), 7.42-7.44 ppm (m, 3H). IR: ν 1622 and 3371 cm^{-1}. MS (ESI): 429.4 (MH^+). $C_{26}H_{24}N_2O_4$ (428.48).

*5.1.56. (1-(A-aminophenyl)-4-phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**14**)*

Synthesized according to general procedure D, starting from **13**. Yield 40% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.70 (s, 3H), 3.76 (s, 6H), 5.27 (s, disappeared after treatment with D_2O, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.35-7.37 (m, 4H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.66 ppm (d, *J* = 2.3 Hz, 1H). IR: ν 1518 and 3350 cm^{-1}. MS (ESI): 429.3 (MH^+). $C_{26}H_{24}N_2O_4$ (428.48).

*5.1.57. (4-(3-Aminophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**39**)*

Synthesized according to general procedure D, starting from **37**. Yield 60%, mp 51-53 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H), 3.81-3.88 (m, 11H; 9H after treatment with D_2O), 6.52 (dd, *J* = 2.0 and 10.8 Hz, 1H), 6.70-6.77 (m, 2H), 7.01-7.38 (m, 8H), 7.54 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 21.47, 56.23, 60.86, 107.40, 113.58, 115.52, 117.87, 119.04, 119.63, 121.50, 123.80, 126.35, 127.78, 128.54, 129.04, 129.65, 134.47, 135.36, 139.50, 140.00, 141.63, 146.24, 152.66, 190.54 ppm. IR: ν 1642 and 3449 cm^{-1}. MS (ESI): 443.3 (MH^+). $C_{27}H_{26}N_2O_4$ (442.51).

*5.1.58. (4-(4-Aminophenyl)-1-(3-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**40**)*

Synthesized according to general procedure D, starting from **38**. Yield 76%, mp 88-89 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 3.81-3.88 (m, 11H; 9H after treatment with D_2O), 6.59 (d, J = 11.2 Hz, 2H), 7.13-7.19 (m, 6H), 7.23-7.26 (m, 2H), 7.32-7.35 (m, 1H), 7.53 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 21.47, 56.20. 60.91, 107.35, 114.89, 117.77, 118,87, 121,40, 123.48, 124.60, 126.33, 127.63, 128.54, 129.49, 129.60, 134.54, 139.53, 139.93, 141.43, 145.17, 152.60 ppm. IR: ν 1578 and 3367 cm^{-1}. MS (ESI): 443.5

(MH^+). $C_{27}H_{26}N_2O_4$ (442.51).

*5.1.59. (1,4-Bis(3-aminophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**47**)*

Synthesized according to general procedure D, starting from **45.** Yield 35% as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.79-3.87 (m, 13H; 9H after treatment with D_2O), 6.50 (d, *J* = 10.4 Hz, 1H), 6.59-6.79 (m, 4H), 7.00-7.26 (m, 6H), 7.49 ppm (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.28, 60.86, 107.12, 107.51, 110.53, 113.57, 115.53, 119.04, 119.68, 122.05, 123.60, 126.43, 128.37, 129.03, 130.62, 134.55, 135.42, 140.56141.74, 146.29, 148.04, 152.70, 190.62 ppm. IR: ν 1579 and 3360 cm^{-1}. MS (ESI): 444.5 (MH^+). $C_{26}H_{25}N_3O_4$ (443.49).

*5.1.60. (1-(3-Aminophenyl)-4-(4-aminophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**48**)*

Synthesized according to general procedure D, starting from **46.** Yield 22%, mp 189-191 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81-3.88 (m, 13H; 9H after treatment with D_2O), 6.58-6.64 (m, 3H), 6.73-6.74 (m, 1H), 6.80-6.83 (m, 1H), 7.10-7.12 (m, 3H), 7.16-7.26 (m, 3H), 7.50 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): *δ* 56.09, 60.90, 107.06, 107.32, 110.61, 113.45, 114.93, 118.88, 118.91, 123.26, 124.73, 126.43, 128.34, 129.52, 130.65, 134.64, 140.64, 145.09, 147.84, 152.56, 152.63, 190.54 ppm. IR: ν 1583 and 2924 cm^{-1}. MS (ESI): 444.3 (MH^+). $C_{26}H_{25}N_3O_4$ (443.49).

*5.1.61 (4-(3-Aminophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**54**)*

Synthesized according to general procedure D, starting from **52.** Yield 56%, mp 135-138 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81-3.87 (m, 14H; 12H after treatment with D_2O), 6.52 (d, *J* = 10.4 Hz, 1H), 6.74-6.77 (m, 2H), 7.01-7.35 (m, 8H), 7.51-7.52 ppm (m, 1H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 20.93, 29.71, 56.23, 60.86, 107.37, 113.57, 115.54, 119.07, 119.70, 120.70, 123.66, 126.41, 128.47, 129.04, 130.36, 130.53, 134.50, 135.39, 136.97, 137.20, 141.58, 146.22, 152.65, 190.51 ppm. IR: ν 1587 and 2921 cm^{-1}. MS (ESI): 443.3 (MH^+). $C_{27}H_{26}N_2O_4$ (442.51).

*5.1.62. (4-(3-aminophenyl)-1-(4-methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**55**)*

Synthesized according to general procedure D, starting from **53.** Yield 85%, mp 181-184 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 3.62 (s, 2H, disappeared after treatment with D_2O), 3.86 (s, 6H), 3.88 (s, 3H), 6.59 (d, *J* = 11.2 Hz, 2H), 7.11-7.35 (m, 9H), 7.51 ppm (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.92, 56.21, 60.92, 107.36, 114.90, 118.95, 120.62, 123.39, 124.70, 126.36, 128.48, 129.52, 130.32, 134.59, 136.81, 137.28, 141.44, 145.13, 152.61, 190.55 ppm. IR: ν 1580 and 3346 cm^{-1}. MS (ESI): 443.4 (MH^+). $C_{27}H_{26}N_2O_4$ (442.51).

*5.1.63. (4-(3-Aminophenyl)-1-(4-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**61**)*

Synthesized according to general procedure D, starting from **59.** Yield 52%, mp 148-150 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80-3.87 (m, 11H; 9H after treatment with D_2O), 6.50-6.53 (m, 1H), 6.67 (s, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.11-7.27 (m, 5H), 7.39-7.44 (m, 2H), 7.48 ppm (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.26, 60.85, 107.52, 113.67, 115.50, 116.58, 116.88, 119.01, 119.79, 122.63, 122.74, 124.08, 126.42, 128.74, 129.09, 134.29, 135.18, 135.89, 135.93, 141.82, 146.30, 152.70, 159.78, 163.05, 190.60 ppm. IR: ν 1641 and 3370 cm^{-1}. MS (ESI): 447.3 (MH^+). $C_{26}H_{23}FN_2O_4$ (446.47).

*5.1.64. (4-(4-Aminophenyl)-1-(4-fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**62**)*

Synthesized according to general procedure D, starting from **60.** Yield 88% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63-3.87 (m, 11H; 9H after treatment with D_2O), 6.58 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 7.11-7.19 (m, 6H), 7.39-7.44 (m, 2H), 7.47 ppm (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.21, 60.91, 107.40, 114.89, 113.52, 116.82, 119.01, 122.51, 122.62, 123.77, 124.38, 126.36, 128.74, 129.49, 134.35, 135.93, 135.97, 141.57, 145.29, 152.63, 159.65, 162.92, 190.56 ppm. IR: ν 1516 and 3366 cm^{-1}. MS (ESI): 447.3 (MH^+). $C_{26}H_{23}FN_2O_4$ (446.47).

*5.1.65. (4-(3-Aminophenyl)-1-(4-aminophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)-methanone (**68**)*

Synthesized according to general procedure D, starting from **66.** Yield 45%, mp 80-82 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.80-3.87 (m, 13H; 9H after treatment with D_2O), 6.50 (d, *J* = 7.8 Hz, 1H), 6.70-6.76 (m, 4H), 7.00-7.08 (m, 2H), 7.11-7.12 (m, 2H), 7.19-7.26 (m, 2H), 7.42-7.43 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.26, 60.84, 107.47, 113.46, 115.60, 115.65, 119.10, 120.17, 122.47, 123.13, 126.84, 128.07, 128.99, 131.19, 134.72, 135.60, 141.59, 145.85, 146.23, 152.66, 190.51 ppm. IR: ν 1578 and 2923 cm^{-1}. MS (ESI): 444.4 (MH^+). $C_{26}H_{25}N_3O_4$ (443.49).

*5.1.66. (1,4-Bis(4-aminophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**69**)*

Synthesized according to general procedure D, starting from **67.** Yield 41% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81-3.87 (m, 13H; 9H after treatment with D_2O), 6.58 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 7.12 (s, 2H), 7.16-7.27 (m, 4H), 7.42 ppm (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.23, 60.39, 60.91, 107.39, 114.91,

115.66, 119.46, 122.43, 122.84, 124.94, 126.83, 128.11, 129.56, 131.36, 134.81, 141.39, 145.04, 145.67, 152.62, 190.57 ppm. IR: ν 1520 and 2923 cm^{-1}. MS (ESI): 444.4 (MH^+). $C_{26}H_{25}N_3O_4$ (443.49).

*5.1.67. General procedure E. Preparation of compounds **71-84**. Example: (E)-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**71**)*

A solution of **70** (1.75 g, 8.3 mmol), benzaldehyde (0.88 g, 8.3 mmol) and NaOH (0.2 g, 4.8 mmol) in ethanol (33 mL) was stirred at room temperature for 24 h. After dilution with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 9:1 as eluent) to furnish **71** (1.0 g, yield 41%), mp 78-80 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 3.94 (s, 6H), 6.89 (s, 2H), 7.52-7.62 (m, 4H), 7.74 (d, *J* = 15.6 Hz, 1H), 8.02-8.05 ppm (m, 2H). IR: ν 1659 and 2941 cm^{-1}.

*5.1.68. (E)-3-(2-chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**72**)*

Synthesized according to general procedure E, starting from **70** and 2-chlorobenzaldehyde. Yield 59%, mp 105-107 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 9H), 7.27-7.65 (m, 6H), 7.73-7.64 (m, 1H), 8.13-8.18 ppm (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.36, 60.99, 106.24, 124.89, 127.11, 127.80, 130.28, 131.17, 133.09, 133.29, 135.37, 140.55, 142.54, 153.15, 189.50 ppm. IR: ν 1657 and 2921 cm^{-1}.

*5.1.69. (E)-3-(4-chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**73**)*

Synthesized according to general procedure E, starting from **70** and 4-chlorobenzaldehyde. Yield 76%, mp 100-102 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 9H), 7.28 (s,

2H), 7.38-7.59 (m, 5H), 7.76 ppm (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.43, 60.99, 106.15, 122.13, 129.24, 129.59, 133.30, 133.39, 136.42, 142.68, 143.20, 153.19, 188.86 ppm. IR: ν 1654 and 2937 cm^{-1}.

*5.1.70. (E)-3-(2-bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**74**)*

Synthesized according to general procedure E, starting from **70** and 2-bromobenzaldehyde. Yield 53%, mp 99-101 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 9H), 7.26-7.36 (m, 5H), 7.63-7.74 (m, 2H), 8.10 ppm (d, *J* = 15.6 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.39, 60.99, 106.33, 125.22, 125.78, 127.74, 127.93, 131.31, 133.06, 133.55, 135.15, 143.07, 153.17, 189.54 ppm. IR: ν 1657 and 2923 cm^{-1}.

*5.1.71. (E)-3-(3-bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**75**)*

Synthesized according to general procedure E, starting from **70** and 3-bromobenzaldehyde. Yield 73%, mp 109-111 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.96 (s, 9H), 7.28-7.33 (m, 3H), 7.44-7.56 (m, 3H), 7.70-7.80 ppm (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.46, 61.00, 106.20, 122.93, 123.10, 127.29, 130.48, 130.79, 133.17, 133.25, 137.04, 142.88, 153.22, 188.71 ppm. IR: ν 1655 and 2942 cm^{-1}.

*5.1.72. (E)-3-(4-bromophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**76**)*

Synthesized according to general procedure E, starting from **70** and 4-bromobenzaldehyde. Yield 71%, mp 120-122 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 9H), 7.27 (s, 2H), 7.44-7.58 (m, 5H), 7.75 ppm (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.42, 61.00, 106.11, 122.20, 124.80, 129.80, 132.21, 133.28, 133.80, 142.65, 143.29, 153.18, 188.88 ppm. IR: ν 1637 and 2838 cm^{-1}.

*5.1.73. (E)-3-(2-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**77**)*

Synthesized according to general procedure E, starting from **70** and 2-nitrobenzaldehyde. Yield 31%, mp 122-124 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95-3.96 (m, 9H), 7.17-7.28 (m, 3H), 7.56-7.61 (m, 1H), 7.70-7.75 (m, 2H), 8.05-8.10 ppm (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.38, 61.00, 106.47, 110.01, 125.00. 127.78, 129.41, 130.32, 132.49, 133.66, 140.04, 142.72, 148.45, 153.21, 190.04 ppm. IR: ν 1657 and 2941 cm^{-1}.

*5.1.74. (E)-3-(3-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**78**)*

Synthesized according to general procedure E, starting from **70** and 3-nitrobenzaldehyde. Yield 59%, mp 139-141 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.96-3.97 (m, 9H), 7.31 (s, 2H), 7.58-7.65 (m, 2H), 7.82-7.94 (m, 2H), 8.25-8.28 (m, 1H), 8.52 ppm (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.52, 61.01, 106.37, 122.38, 124.36, 124.64, 130.05, 132.87, 134.36, 136.74, 141.58, 143.12, 148.79, 153.32, 190.01 ppm. IR: ν 1720 and 2928 cm^{-1}.

*5.1.75. (E)-3-(4-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**79**)*

Synthesized according to general procedure E, starting from **70** and 4-nitrobenzaldehyde. Yield 89%, mp 170-175 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.77 (s, 3H), 3.90 (s, 6H), 7.45 (s, 2H), 7.82 (d, *J* = 15.6 Hz, 1H), 8.11-8.20 (m, 3H), 8.28-8.30 ppm (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.49, 61.03, 106.34, 124.21, 125.44, 128.95, 132.78, 141.08, 141.40, 143.16, 148.56, 153.30, 188.26 ppm. IR: ν 1653 and 3189 cm^{-1}.

*5.1.76. (E)-3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**80**)*

Synthesized according to general procedure E, starting from **70** and 4-methoxybenzaldehyde. Yield 84%, mp 92-94 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 3H), 3.94-3.95 (m, 9H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.27 (s, 2H), 7.35-7.40 (m, 1H), 7.61 (d, *J* = 8.7, 2H), 7.79 ppm (d, *J* =15.6 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 55.41, 56.37, 60.97, 105.82, 105.98,

114.42, 119.39, 127.60, 130.24, 133.82, 142.27, 144.62, 153.11, 161.69, 189.24 ppm. IR: ν 1655 and 2970 cm^{-1}.

*5.1.77. (E)-3-(5-bromo-2-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**81**)*

Synthesized according to general procedure E, starting from **70** and 5-bromo-2-methoxybenzaldehyde. The product was used without further purification.

*5.1.78. (E)-3-(2,5-difluorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**82**)*

Synthesized according to general procedure E, starting from **70** and 2,5-difluorobenzaldehyde. The product was used without further purification.

*5.1.79. (2E,4E)-5-phenyl-1-(3,4,5-trimethoxyphenyl)penta-2,4-dien-1-one (**83**)*

Synthesized according to general procedure E, starting from **70** and *trans*-cinnamaldehyde. Yield 36% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.75 (s, 3H), 3.88 (s, 6H), 7.24-7.26 (m, 2H), 7.33 (s, 2H), 7.35-7.37 (m, 1H), 7.40-7.43 (m, 2H), 7.50-7.51 (m, 2H), 7.58-7.60 ppm (m, 2H). IR: ν 1650 and 2943 cm^{-1}.

*5.1.80. (E)-3-(2-fluorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**84**)*

Synthesized according to general procedure E, starting from **70** and 2-fluorobenzaldehyde. Yield 65%, mp 115-117 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94-3.95 (m, 9H), 7.11-7.27 (m, 2H), 7.29-7.43 (m, 3H), 7.57-7.68 (m, 2H), 7.90 ppm (d, *J* = 15.9 Hz, 1H). IR: ν 1648 and 2931 cm^{-1}.

*5.1.81. (E)-3-(o-tolyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**85**)*

Synthesized according to general procedure E, starting from **70** and 2-methylbenzaldehyde, but reaction time was 2 h. Yield 81%, mp 107-109 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300

MHz): δ 2.49 (s, 3H), 3.95 (s, 9H), 7.24-7.42 (m, 6H), 7.69 (d, *J* = 5.7 Hz, 1H), 8.11 ppm (d, *J* = 11.7 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 19.88, 56.21, 56.40, 60.98, 106.19, 123.06, 126.35, 126.43, 130.26, 130.94, 133.52, 134.04, 138.30, 142.37, 153.18, 189.23 ppm. IR: ν 1655 and 3019 cm^{-1}.

*5.1.82. (E)-3-(3-chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**86**)*

Synthesized according to general procedure E, starting from **70** and 3-chlorobenzaldehyde, but reaction time was 2 h. Yield 75%, mp 100-102 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 3H), 3.96 (s, 6H), 7.28-7.50 (m, 6H), 7.71 ppm (t, *J* = 15 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.43, 60.99, 106.15, 110.02, 122.88, 126.86, 127.85, 130.22, 130.33, 133.16, 134.96, 136.74, 142.97, 153.20, 188.72 ppm. IR: ν 1665 and 2945 cm^{-1}.

*5.1.83. (E)-3-(2-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**87**)*

Synthesized according to general procedure E, starting from **70** and 2-methoxylbenzaldehyde, but reaction time was 2 h. Yield 29% as and oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.62-3.95 (m, 12H), 6.94-7.03 (m, 2H), 7.28 (s, 2H), 7.39 (t, *J* = 6 Hz, 1H), 7.55 (d, *J* = 12 Hz, 1H), 7.64 (d, *J* = 5.7 Hz, 1H), 8.11 ppm (d, *J* = 12 Hz, 1H). IR: ν 1575 and 2940 cm^{-1}.

*5.1.84. (E)-3-(3-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**88**)*

Synthesized according to general procedure E, starting from **70** and 3-methoxylbenzaldehyde, but reaction time was 2 h. Yield 87% as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H), 3.94-3.95 (m, 9H), 6.96-6.99 (m, 1H), 7.16-7.17 (m, 1H), 7.21-7.27 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 15.6 Hz, 1H), 7.78 ppm (d, *J* = 15.9 Hz, 1H). IR: ν 1575 and 2940 cm^{-1}.

*5.1.85. (E)-3-(2,4,6-trifluorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**89**)*

Synthesized according to general procedure E, starting from **70** and 2,4,6-

trifluorobenzaldehyde, but reaction time was 2 h. Yield 68%, mp 107-109 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86-3.95 (m, 9H), 6.74-6.80 (m, 2H), 7.28 (s, 2H), 7.71-7.85 ppm (m, 2H). IR: ν 1660 and 3079 cm^{-1}.

*5.1.86. General procedure F. Preparation of compounds **90-108**. Example: (4-Phenyl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**90**)*

A mixture of **71** (0.20 g; 0.67 mmol) and *p*- TosMIC (0.13 g, 0.67 mmol) in DMSO/Et_2O 1:2 (6.0 mL) was added dropwise into a well stirred suspension of NaH (60% in mineral oil, 0.09 g, 2.98 mmol) in dry Et_2O (3.5 mL) under an Ar stream. The reaction mixture was stirred at room temperature for 4 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and filtered. Removal of the solvent gave a residue that was purified by column chromatography (silica gel, *n*-hexane:ethyl acetate 1:1 as eluent) to furnish **90** (0.16 g, 70%), mp 179-181 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 6H), 3.84 (s, 3H), 6.64-6.65 (m, 2H), 6.93-6.95 (m, 1H), 7.28-7.29 (m, 1H), 7.35-7.39 (m, 2H), 7.46-7.48 (m, 1H), 7.78-7.81 (m, 2H), 8.82 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1617 and 3285 cm^{-1}. MS (ESI): 366.2 (MH^+). $C_{21}H_{19}NO_5$ (365.38).

*5.1.87. (4-(2-Methylphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**91**)*

Synthesized according to general procedure F, starting from **85**. Yield 55%, mp 206-208 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 3.82 (s, 6H), 3.87 (s, 3H), 6.71 (s, 1H), 7.04-7.26 (m, 7H), 9.11 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1625 and 3235 cm^{-1}. MS (ESI): 380.3 (MH^+). $C_{22}H_{21}NO_5$ (379.41).

*5.1.88. (4-(2-Chlorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**92**)*

Synthesized according to general procedure F, starting from **72**. Yield 98%, mp 177-179 °C

(from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H), 3.87 (s, 3H), 6.85 (s, 1H), 7.06-7.33 (m, 7H), 9.34 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 56.19, 60.88, 107.00, 119.85, 123.24, 125.54, 126.39, 127.93, 129.46, 131.73, 133.33, 134.13, 134.67, 141.21, 152.59, 190.73 ppm. IR: ν 1625 and 3235 cm^{-1}. MS (ESI): 372.6 (MH^+). $C_{20}H_{18}ClNO_4$ (371.81).

*5.1.89. (4-(3-Chlorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**93**)*

Synthesized according to general procedure F, starting from **86**. Yield 74%, mp 154-156 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H), 3.87 (s, 3H), 6.85 (s, 1H), 7.06-7.31 (m, 7H), 9.42 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.20, 60.92, 107.17, 119.05, 121.75, 125.45, 126.25, 126.79, 126.98, 128.51, 129.22, 133.77, 134.77, 136.70, 141.45, 152.69, 190.93 ppm. IR: ν 1625 and 3235 cm^{-1}. MS (ESI): 372.8 (MH^+). $C_{20}H_{18}ClNO_4$ (371.81).

*5.1.90. (4-(4-Chlorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**94**)*

Synthesized according to general procedure F, starting from **73**. Yield 82%, mp 217-219 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.04-7.13 (m, 3H), 7.28-7.40 (m, 5H), 11.68 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, DMSOd_6): *δ* 55.77, 60.00, 106.59, 119.68, 120.33, 124.08, 127.53, 127.72, 129.85, 130.08, 134.19, 134.72, 140.49, 152.26, 189.05 ppm. IR: ν 1625 and 3235 cm^{-1}. MS (ESI): 372.6 (MH^+). $C_{20}H_{18}ClNO_4$ (371.81).

*5.1.91. (4-(2-Bromophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**95**)*

Synthesized according to general procedure F, starting from **74**. Yield 80%, mp 188-190 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.71 (s, 3H), 3.79 (s, 6H), 6.99 (s, 3H), 7.11-

7.17 (m, 1H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.42 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 11.63 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.76, 59.93, 106.36, 109.45, 119.99, 121.79, 123.71, 123.97, 125.87, 126.91, 127.84, 131.86, 132.01, 134.57, 136.88, 140.25, 152.20, 188.45 ppm. IR: ν 1642 and 3397 cm^{-1}. MS (ESI): 417.2 (MH^+). $C_{20}H_{18}BrNO_4$ (416.27).

*5.1.92. (4-(3-Bromophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**96**)*

Synthesized according to general procedure F, starting from **75**. Yield 48%, mp 155-157 °C (from ethanol). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.03 (s, 2H), 7.18-7.23 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 11.74 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.73, 59.93, 106.54, 120.05, 120.37, 120.96, 123.77, 127.09, 127.82, 128.13, 129.70, 130.68, 134.70, 137.73, 140.44, 152.26, 189.10 ppm. IR: ν 1578 and 3226 cm^{-1}. MS (ESI): 417.1 (MH^+). $C_{20}H_{18}BrNO_4$ (416.27).

*5.1.93. (4-(4-Bromophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**97**)*

Synthesized according to general procedure F, starting from **76**. Yield 88%, mp 155-157 °C (from ethanol). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.72 (s, 3H), 3.78 (s, 6H), 7.04 (s, 2H), 7.13 (s, 1H), 7.28-7.44 (m, 5H), 11.70 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, DMSOd_6): δ 55.75, 60.00, 106.55, 118.53, 119.67, 120.26, 124.10, 127.77, 130.21, 130.44, 134.55, 134.69, 140.45, 152.25, 189.01 ppm. IR: ν 1577 and 2922 cm^{-1}. MS (ESI): 417.2 (MH^+). $C_{20}H_{18}BrNO_4$ (416.27).

*5.1.94. (4-(2-Nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**98**)*

Synthesized according to general procedure F, starting from **77**. Yield 41%, mp 122-124 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H), 3.87 (s, 3H), 6.82 (s, 1H), 7.02 (s,

2H), 7.22 (s, 1H), 7.27-7.53 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H), 9.55 (br, s, disappeared after treatment with D_2O, 1H) ppm. IR: ν 1523 and 2939 cm^{-1}. MS (ESI): 383.3 (MH^+). $C_{20}H_{18}N_2O_6$ (382.37).

*5.1.95. (4-(3-Nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**99**)*

Synthesized according to general procedure F, tarting from **78**. Yield 54%, mp 172-175 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.85 (s, 6H), 3.89 (s, 3H), 6.98-6.99 (m, 1H), 7.09 (s, 2H), 7.29-7.31 (m, 1H), 7.43 (t, *J* = 9 Hz, 1H), 7.71-7.75 (m, 1H), 8.01-8.05 (m, 1H), 8.21-8.23 (m, 1H), 9.39 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 56.28, 60.96, 107.21, 119.84, 120.97, 121.45, 123.34, 124.55, 127.89, 128.82, 134.88, 134.98, 137.04, 141.50, 148.04, 152.78, 191.11ppm. IR: ν 1522 and 3308 cm^{-1}. MS (ESI): 383.3 (MH^+). $C_{20}H_{18}N_2O_6$ (382.37).

*5.1.96. (4-(4-Nitrophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**100**)*

Synthesized according to general procedure F, starting from **79**. Yield 27%, mp 175-180 °C (from ethanol). ^1H NMR (DMSO-d_6, 400 MHz): δ 3.71 (s, 3H), 3.79 (s, 6H), 7.07 (s, 2H), 7.34 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.59-7.62 (m, 2H), 8.10-8.13 (m, 2H), 11.87 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1633 and 3195 cm^{-1}. MS (ESI): 383.2 (MH^+). $C_{20}H_{18}N_2O_6$ (382.37).

*5.1.97. (4-(2-Methoxyphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**101**)*

Synthesized according to general procedure F, starting from **87**. Yield 54%, mp 167-169 °C (from ethanol). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.49 (s, 3H), 3.74 (s, 6H), 3.83 (s, 3H), 6.64 (d, *J* = 6 Hz, 1H), 6.85-6.91 (m, 2H), 7.04 (s, 2H), 7.11-7.15 (m, 1H), 7.26-7.29 (m, 2H), 9.26 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1625 and 2931 cm^{-1}. MS (ESI): 368.2

(MH^+). $C_{21}H_{21}NO_5$ (367.40).

*5.1.98. (4-(3-Methoxyphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**102**)*

Synthesized according to general procedure F, starting from **88**. Yield 62%, mp 155-157 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.69 (s, 3H), 3.79 (s, 6H), 3.87 (s, 3H), 6.68-6.72 (m, 1H), 6.84-6.86 (m, 2H), 6.90-6.93 (m, 1H), 7.08 (s, 2H), 7.12-7.26 (m, 2H), 9.39 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1629 and 3182 cm^{-1}. MS (ESI): 368.3 (MH^+). $C_{21}H_{21}NO_5$ (367.40).

*5.1.99. (4-(4-Methoxyphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**103**)*

Synthesized according to general procedure F, starting from **80**. Yield 81%, mp 139-142 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H), 3.81 (s, 6H), 3.88 (s, 3H), 6.79 (d, *J* = 9 Hz, 3H), 7.09 (s, 2H), 7.22-7.29 (m, 3H), 9.15 ppm (br, s, disappeared after treatment with D_2O, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 55.21, 56.16, 60.92, 107.18, 113.52, 118.12, 121.61, 126.40, 126.59, 127.23, 129.64, 134.82, 141.27, 152.58, 158.23, 190.94 ppm. IR: ν 1627 and 2922 cm^{-1}. MS (ESI): 368.3 (MH^+). $C_{21}H_{21}NO_5$ (367.40).

*5.1.100. (4-(5-Bromo-2-methoxyphenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**104**)*

Synthesized according to general procedure F, starting from **81**. Yield 58% as an oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.40 (s, 3H), 3.65 (s, 3H), 3.70 (s, 6H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 2H), 6.99 (d, *J* = 1.9 Hz, 1H), 7.23-7.26 (m, 1H), 7.33-7.34 (m, 2H), 11.59 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1627 and 2922 cm^{-1}. MS (ESI): 447.2 (MH^+). $C_{21}H_{20}BrNO_5$ (446.29).

*5.1.101. (4-(2,5-difluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**105**)*

Synthesized according to general procedure F, starting from **82**. Yield 36%, mp 202-205 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.71 (s, 3H), 3.77 (s, 6H), 7.02 (s, 2H), 7.03-7.13 (m, 3H), 7.14-7.20 (m, 1H), 7.44-7.45 (m, 1H), 11.75 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1654 and 2950 cm^{-1}. MS (ESI): 374.3 (MH^+). $C_{20}H_{17}F_2NO_4$ (373.35).

*5.1.102. (4-(2,4,6-trifluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**106**)*

Synthesized according to general procedure F, starting from **89**. Yield 65%, mp 221-223 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64-3.87 (m, 9H), 6.63 (t, *J* = 8.4 Hz, 2H), 6.96 (s, 1H), 7.05 (s, 2H), 7.34-7.36 (m, 1H), 10.84 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1581 and 3249 cm^{-1}. MS (ESI): 392.3 (MH^+). $C_{20}H_{16}F_3NO_4$ (391.34).

*5.1.103. (E)-(4-Styryl-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**107**)*

Synthesized according to general procedure E, starting from **83**. Yield 51%, mp 112-115 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.74 (s, 3H), 3.82 (s, 6H), 6.98 (d, *J* = 16.7 Hz, 1H), 7.04 (s, 2H), 7.19-7.20 (m, 1H), 7.32-7.35 (m, 2H), 7.37 (s, 2H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.61 (d, *J* = 16.6 Hz, 1H), 11.67 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1650 and 3025 cm^{-1}. MS (ESI): 364.2 (MH^+). $C_{22}H_{21}NO_4$ (363.41).

*5.1.104. (4-(2-Fluorophenyl)-1H-pyrrol-3-yl)(3,4,5-trimethoxyphenyl)methanone (**108**)*

Synthesized according to general procedure F, starting from **84**. Yield 55%, mp 101-103 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 6H), 3.85 (s, 3H), 6.93-6.99 (m, 2H), 7.02-7.07 (m, 3H), 7.12-7.17 (m, 1H), 7.27-7.32 (m, 2H), 8.82 ppm (br, s, disappeared after treatment with D_2O, 1H). IR: ν 1579 and 3257 cm^{-1}. MS (ESI): 356.2 (MH^+). $C_{20}H_{18}FNO_4$ (355.36).

5.2. Molecular Modeling

All molecular modeling studies were performed on a MacPro dual 2.66GHz Xeon running Ubuntu 14LTS. The tubulin structure was downloaded from the PDB data bank (http://www.rcsb.org/), PDB code: 1SA0 [13]. Ligand structures were prepared with Maestro [40]. Proteins were prepared by Protein Preparation Wizard [41] of Maestro. The docking simulations were performed using PLANTS [42]. Images shown in the manuscript were prepared with Pymol [43].

5.3. Biology

5.3.1. Tubulin assembly and colchicine binding assays

The assembly reaction mixtures contained 0.8 M monosodium glutamate (pH 6.6 with HCl in a 2 M stock solution), 10 μM tubulin, 4% (v/v) DMSO, and varying concentrations of drug. Following a 15 min preincubation at 30 °C, samples were chilled on ice, GTP to 0.4 mM was added, and turbidity development was followed at 350 nm in a temperature-controlled recording spectrophotometer for 20 min at 30 °C. The extent of reaction was measured. Full experimental details were previously described [44]. For the colchicine binding assay, reaction mixtures contained 1.0 μM tubulin, 5.0 μM [^{3}H]colchicine, and 5.0 μM inhibitor and were incubated for 10 min at 37 °C. Complete details were described previously [45]. As a tubulin assembly inhibitor, colchicine yielded an IC_{50} of 3.2 ± 0.4 μM. For the tubulin assembly data described here, different tubulin preparations were used. The contemporaneous CSA4 controls yielded IC_{50}'s ranging from 0.54 ± 0.06 μM to 1.2 ± 0.1 μM. Compound **1** yielded an IC_{50} of 1.2 ± 0.1 μM. Colchicine, CSA4 and **1** inhibited the growth of the MCF-7 cells (obtained from the National Cancer Institute drug screening program) with IC_{50} values of 5.0 ± 1, 13 ± 3 and 9.0 ± 2 nM, respectively.

5.3.2. Cell cultures

Cell lines were obtained from the American Type Culture Collection (ATCC), Rockville MD, unless otherwise specified. U343MG, U87MG and T98G cell lines were obtained from the National Institute for Cancer Research of Genoa (Italy). All cell lines, except as indicated, were grown in Dulbecco's modified Eagle's medium (DMEM) (RPMI-1640 medium for the SK-N-BE and SK-N-BE(2)-C cells) supplemented with 10% fetal bovine serum (FBS), 20 mM HEPES, 100 U/mL penicillin, 100 mg/mL streptomycin, and 1% L-glutamine; an additional specific component was the addition of glucose (4.5 g/L for HT29 and HCT116 cells). Cell lines were cultured at 37 °C in 5% CO_2/95% air in a humidified incubator. Treatments were initiated 24 h after cell seeding using compounds **42**, **44**, **48**, **62** and **69** diluted in 0.1% DMSO, the indicated reference compound, or 0.1% DMSO vehicle, for 24-72 h, as indicated. T98G and U87MG cells were cultured in RPMI medium and minimum essential Eagle's medium, respectively, supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin and 1% non-essential amino acids at 37 °C in 5% CO_2. The U343MG cells were cultured in minimum essential Eagle's medium with 2 mM L-glutamine and Earle's BSS adjusted to contain 1.5 mg/mL sodium bicarbonate and supplemented with 10% FBS, 100 U/mL penicillin, 100 mg/mL streptomycin, 1% non-essential amino acids and 1.0 mM sodium pyruvate at 37 °C in 5% CO_2. KBM5, KU812, and LAMA84 cell lines expressing the IM-sensitive wild type BCR/ABL were derived from CML patients in blast crisis [46]. These CML cell lines were purchased from ATCC and cultured in RPMI-1640 (Life Technologies, Gaithersburg, MD) containing 10% FBS (Cambrex, Baltimore, MD), 100 units/mL penicillin, 100 μg/mL streptomycin, 2 mM L-glutamine (GibcoBRL, Paisley, UK) at 37 °C with a 5% CO_2 atmosphere. KBM5-T315I cells ectopically expressing the IM-resistant T315I mutation of BCR-ABL were

also from ATCC and maintained in the presence of IM at 1.0 μM. PBMCs were obtained after informed consent from 2 healthy donors and purified by standard Ficoll-Hypaque density gradient centrifugation (Amersham Biosciences, Uppsala, Sweden). IM was kindly provided by Novartis (Basel, Switzerland) or synthesized by Dr Alfonso Zambon (University of Venezia, Italy). Stock solutions of IM at 1 or 10 mM in sterile water were filtered and stored at -20 °C.

5.3.3. Cell viability assay

The methodology for the evaluation of the growth of human MCF-7 breast carcinoma cells was previously described, except that cells were grown for 96 h for IC_{50} determinations [47]. Cell viability of KU812, LAMA84-S, LAMA84-R, KBM5-WT, KBM5-T315I, HT29, HCT116, SW480, SW620, T24, ES-2, SK-N-BE and SK-N-BE(2)-C cells was determined using the MTT colorimetric assay [48]. The cells were seeded into 24-well plates to a density of 15×10^3/mL in each well. After 24 h of growth to allow attachment of cells to the wells, test compounds were added at 20-320 nM. After 48 h of growth and removal of the culture medium, 500 μL/well of PBS containing 500 μM MTT was added. Cell cultures were further incubated at 37 °C for 2 h in the dark. The solutions were then gently aspirated from each well, and the formazan crystals within the cells were dissolved in propan-2-ol and 0.04 N HCl (200 μL). Optical densities were read at 550 nm using a Multiskan Spectrum Thermo Electron Corporation reader. The results were expressed as % relative to vehicle-treated control (0.1% DMSO), and IC_{50} values were calculated by nonlinear regression analysis (GraphPad Prism statistics software). Experiments were performed in triplicate. The effect of treatment with compounds **42**, **44**, **48**, **62** and **69** on the T98G, U87MG and U343MG cell lines was estimated using the colorimetric MTS conversion assay, as previously reported [49]. After compound incubation, the MTS reagent was added, and the absorbance at 590 nm was measured by a microplate reader (Wallac, Victor 2,

1420 Multilabel Counter, PerkinElmer). The percentage of proliferating cells after compound exposure was calculated with respect to control cells (100%).

5.3.4. Statistical analyses

Graph-Pad Prism 5 software (Graph-Pad Software Inc, San Diego, CA) was used for data analysis and graphic presentations. Statistical analysis was performed by non-linear regression fitting; sigmoidal-dose response curves were generated using the log(inhibitor) vs response analysis. The IC_{50} value and the maximal efficacy of compounds in inhibiting cell viability (E max) were derived.

5.4. In vivo experiments

5.4.1. Xenograft model

Briefly, 8 week-old female BALB/$C^{nu/nu}$ mice (20 mice) were purchased from the Shanghai University of Traditional Chinese Medicine with Institutional Animal Care and Use Committee approval in accordance with institutional guidelines. The mice were randomly divided into four groups. In group #1 (5 mice), 1×10^8 cells/mL of EZ-2 in logarithmic growth phase were harvested and inoculated subcutaneously and intraperitoneal injection of 100 μL **48** (20 mg/kg) was administered every 2 days. In group #2 (5 mice), 1×10^8 cells/mL of EZ-2 in logarithmic growth phase were harvested and inoculated subcutaneously, and intraperitoneal injection of 100 μL saline was administered every 2 days. In group #3 (5 mice), 1×10^8 cells/mL of T24 in logarithmic growth phase were harvested and inoculated subcutaneously, and intraperitoneal injection of 100 μL **48** (20 mg/kg) was administered every 2 days. In group #4 (5 mice), 1×10^8 cells/mL of T24 in logarithmic growth phase were harvested and inoculated subcutaneously, and intraperitoneal injection of 100 μL saline was administered every 2 days. After 40 days, the mice were sacrificed, and the tumors were removed. The tumors were weighed, and the volumes were

calculated using the following formula: tumor volume (cm^3) = (ab^2)/2 (a: the longest axis (cm), b: the shortest axis (cm)).

5.4.2. Hematoxylin and eosin staining

Tissue samples were fixed in 4% paraformaldehyde, dehydrated, and embedded in paraffin. The paraffin-embedded tissues were cut into 4 μm sections using a microtome, and the sections were affixed onto glass slides. Subsequently, the sections were dewaxed using xylene and subjected to dehydration in an ethanol gradient. The sections were stained with hematoxylin (H) for 5 min at room temperature, and then 1% ethanol was added for 30 s. Afterwards, aqueous ammonia was added for 1 min, followed by rinsing in distilled water for 5 min. Subsequently, the sections were stained with eosin (E) for 2 min at room temperature and then rinsed with distilled water for 2 min. Then, decolorization with an ethanol gradient was performed, and xylene was added for 2 min for clearing. Finally, the sections were sealed and mounted with neutral resin.

5.4.3. Immunofluorescence staining

Briefly, fresh tissues were immersed in 4% paraformaldehyde (Sigma-Aldrich) for fixation at room temperature for 30 min. The tissues were then dehydrated with an ethanol gradient, embedded in paraffin, sectioned (thickness: 6 μm), and immersed in xylene for dewaxing. Tissue sections were blocked with immunohistochemical blocking solution (Beyotime Biotechnology Co., Ltd., Zhejiang, China) at 37 °C for 30 min. The blocking solution was then discarded, and the sections were washed three times at room temperature for 5 min each with immunohistochemical washing solution (Beyotime Biotechnology). Then, primary antibodies [Ki-67 (D3B5) rabbit mAb, Bax (D2E11) rabbit mAb, Bcl-2 (D55G8) rabbit mAb, CD31 (PECAM-1) (D8V9E) XP® rabbit mAb, caspase-3 antibody, caspase-9 antibody, Cell Signaling

Technology, MA, USA] were added and incubated at 37 °C for 45 min. After incubation, the antibody solution was discarded, and the sections were washed three times at room temperature for 5 min each with immunohistochemical washing solution (Beyotime Biotechnology). Then, secondary antibodies [goat anti-rabbit IgG H&L (Alexa Fluor® 532), Abcam, MA, USA] were added, and the tissues were incubated at 37 °C for 45 min. After incubation, the antibody solution was discarded, and the sections were washed three times at room temperature for 5 min each with immunohistochemical washing solution. Finally, immunofluorescence blocking solution (Sigma-Aldrich) was added, and the sections were mounted.

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Disclaimer

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at the Journal website.

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Manuscript title: Structure-Activity Relationship Studies and *in Vitro* and *in Vivo* Anticancer Activity of Novel 3-Aroyl-1,4-diarylpyrroles against Solid Tumors and Hematological Malignancies

Research Highlights

- Novel 3-aroyl-1,4-diarylpyrrole derivatives were synthesized
- The 1- and 4-aminophenyl rings correlated with potent antitumor activity
- Compound **69** was superior to nilotinib and imatinib in resistant CML cells
- **48** potently inhibited glioblastoma, colorectal and urinary bladder cancer cell lines
- In animal models, **48** inhibited of the growth of T24 and ES-2 carcinoma tumors

Declaration of Interest Statement

We designed and synthesized a series of new 3-aroyl-1,4-diarylpyrrole derivatives. Structure-activity relationship studies highlighted a key role of amino phenyl rings at positions 1 and 4 of the pyrrole ring for the antitumor activity. Beside the potent antitumor activity displayed by this series, we envisaged two different anticancer profiles: as inhibitors of glioblastoma, colorectal and urinary bladder cancer cell lines (represented by **48**) or CML cell lines (represented by **69**). These two compounds pave the way to designing of new broad-spectrum anticancer agents active in different types of solid and hematological tumors.