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Synthesis and antileukemic activity of new 3-(1-phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolin-4(3H)-ones

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Abstract

3-(1-Phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolin-4(3H)-ones **14a–q** and **15a–q** were synthesized by refluxing in acetic acid the corresponding 2-methylquinazolinones **12** and **13** with the opportune benzoic aldehyde for 12 h. The synthesized styrylquinazolinones **14a–q** and **15a–q** were tested in vitro for their antileukemic activity against L1210 (murine leukemia), K562 (human chronic myelogenous leukemia) and HL60 (human leukemia) cell lines showing in some cases good activity.

Keywords: 3-(1-Phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolin-4(3H)-ones; Antileukemic activity

1. Introduction

Some years ago, we synthesized and evaluated for their antifungal activity some 3-(3-methyl-5-isoxazolyl)-2-styryl-quinazolin-4(3H)-ones **1a–f** [1](Fig. 1).

In the literature it was reported that quinazolinone derivatives are very interesting drugs with antiproliferative activity, known to bind to the colchicine site on tubulin and interfering with its polymerization [2,3]. Among these, 2-aryl and 2-styrylquinazolin-4(3H)-ones **2** and **3** (Fig. 1) are two of the best representative examples of antimitotic quinazolinones [4–6]. In particular, Jiang et al. [6] first studied in depth this antimitotic heterocyclic class showing that the inhibitory activity was only retained if the intact 2-styrylquinazolinone structure **3** was present and enhanced by small hydrophobic substituent at the 6 position.

Owing to the antitumoral activity described for the styrylquinazolinone derivatives of type **3** we preliminarily tested some of the compounds **1** for their cytotoxic activity against L1210 murine leukemia and K562 human chronic myeloid leukemia. Among them, only the **1b** and **1e** showed moderate cytotoxicity at 1 μg/ml which was 35.4% inhibition against K562 cells for **1b** and 19.0% inhibition against L1210 cells for **1e**.

To improve the above-mentioned activity we thought to modify the structure of compounds **1** both by changing the isoxazole moiety with an other heterocyclic system and by replacing the styryl moiety with different groups.

In particular, since some pyrazole derivatives having antiproliferative activity are known [7,8], we substituted the *N*-3 isoxazole with the 1-phenyl-3-methylpyrazol-5-yl moiety.

Moreover, SAR studies have shown that one of the important structural features of colchicine **4** for binding to tubulin is the methoxy groups of the A ring and the carbonyl of C ring. Therefore, the colchicine binding can proceed by two step process: initial stacking interaction with colchicine ring C followed by slow conformational change of tubulin allowing the further binding of ring A [9].

2-Styrylquinazolinones 3 and all the others antimitotic agents that bind to the colchicine site, such as 2,3,4-trimethoxy-4′-carbomethoxy-1-1′-diphenyl (TBC) [10] **5**, podophyllotoxin [11] **6** and combretastatin A-4 [12] **7**, generally share homology with the A and C rings of colchicine **4**. This common feature, called “biaryl system”, is formed by two aromatic or heteroaromatic systems directly bonded or separated by one to four carbon atoms in such way that they are close in the space but out of coplanarity [13]; usually one of these aromatic system is trimethoxy substituted.

Based on the idea that both the quinazolinone system and the styryl moiety of compounds **3** could be compared to the C

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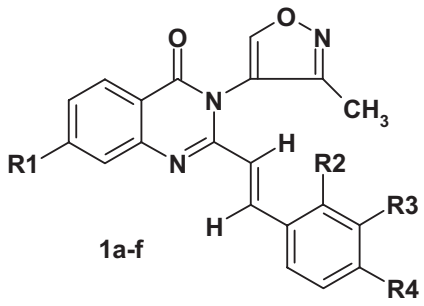
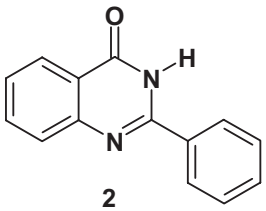


	R1	R2	R3	R4
a	H	H	H	H
b	H	H	H	Cl
c	H	H	NO_2	H
d	Cl	H	H	H
e	Cl	NO_2	H	H
f	Cl	H	H	Cl



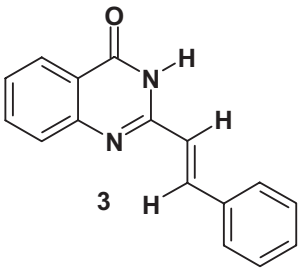
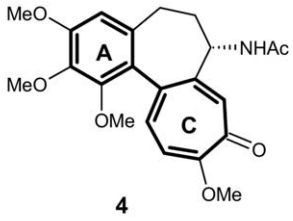
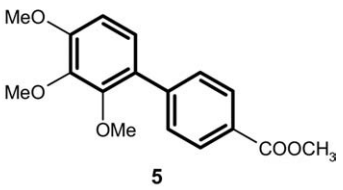


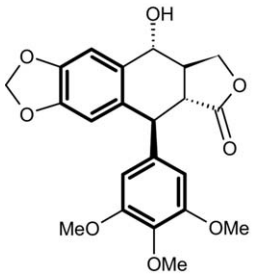
Fig. 1. Structural formulas of compounds **1a–f, 2** and **3**.

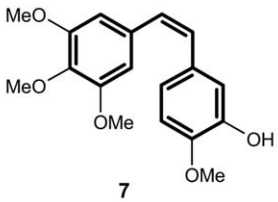
and A rings of colchicine, respectively (Fig. 2), we carried out the synthesis of the mono-, di- and trimethoxy 2-styrylquinazolinones **14** and **15**.

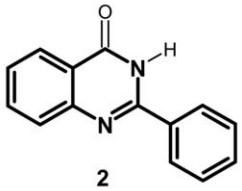
Moreover, a methyl group in the 2′, 3′ and 4′ positions and the substituents of the active derivatives **1b** and **1e** (2′-Cl and 4′-NO_2, respectively) were also introduced.











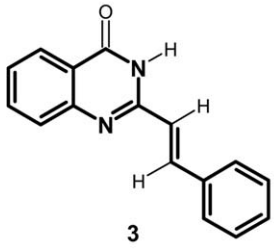
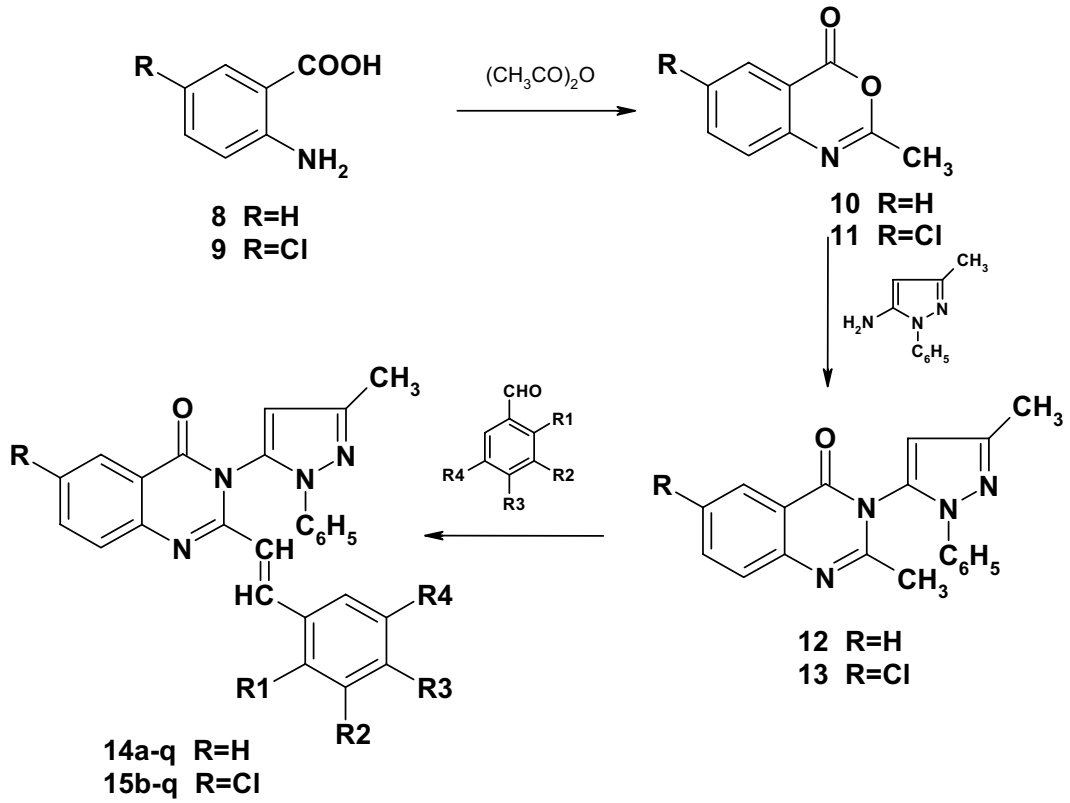


Fig. 2. Representative examples of antineoplastic bridged biaryls.



	a	b	c	d	e	f	g	h	i	l	m	n	o	p	q
R1	H	OCH_3	H	H	OCH_3	OCH_3	H	H	OCH_3	CH_3	H	H	NO_2	H	H
R2	H	H	OCH_3	H	H	OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	H	H	H	OH
R3	H	H	H	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3	H	H	CH_3	H	Cl	OCH_3
R4	H	H	H	H	H	H	H	OCH_3	H	H	H	H	H	H	H

Scheme 1. General synthetic route to 3-(1-phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolinones **14a–q** and 6-chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolinones **15b–q**.

2. Chemistry

3-(1-Phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolinones **14a–q** and 6-chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolinones **15b–q** were obtained starting from 2-methylquinazolinones **12** and **13** by condensation with the opportune benzaldehyde (Scheme 1); the reaction was performed by refluxing equimolar amounts of 2-methylquinazolinones **12** and **13** and benzaldehyde in glacial acetic acid [14].

The structures of new compounds were elucidated by analytical as well as spectroscopic measurements. In particular, ^{1}H-NMR spectra of compounds **14** and **15** are consistent with an *E*-olefinic structure [15]: β-olefinic protons appeared as doublets at δ 6.09–6.80 (J = 15 Hz as requested for a *E* geometry) while the α-olefinic hydrogens were found along with aromatic multiplet because of the deshielding of two quinazolinone nitrogens.

3-(1-Phenyl-3-methylpyrazol-5-yl)-2-methylquinazolinone **12** was known [16]. 6-Chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-methylquinazolinone **13** were obtained by fusion of the 6-chloro-2-methylbenzoxazin-4(3H)-one **11** [17] with 1-phenyl-3-methyl-5-aminopyrazole according with the Scheme 1.

3. Biological results and discussion

The synthesized styrylquinazolinones **14a–q** and **15b–q** were tested in vitro for their antileukemic activity against L1210 (murine leukemia), K562 (human chronic myelogenous leukemia) and HL60 (human leukemia) cell lines. Colchicine **4**, whose antileukemic activity is well known, was used as reference compound.

The percent of growth inhibition at screening concentration of 1 μg/ml and the IC_{50} values for compounds that exhibited at least 50% of growth inhibition are reported in Tables 1 and 2, respectively.

Several 2-styrylquinazolinones demonstrated antileukemic activity against the above-mentioned cell lines, although

Table 1
Percent growth inhibition recorded on K562, HL60 and L1210 cell lines at 1 μg/ml concentration of **14a–q** and **15b–q** compounds

Compounds	K562	HL60	L1210
14a	ns	ns	50.0
14b	ns	ns	87.0
14c	ns	26.0	79.0
14d	ns	ns	32.5
14e	ns	ns	73.5
14f	23.3	37.6	79.3
14g	ns	37.0	60.0
14h	20.0	ns	74.5
14i	47.5	44.3	57.6
14l	44.6	53.5	57.6
14m	48.2	ns	62.0
14n	46.0	27.0	ns
14o	ns	33.5	66.1
14p	29.4	ns	23.3
14q	20.0	ns	25.0
15b	ns	ns	ns
15c	ns	ns	ns
15d	ns	ns	ns
15e	31.5	ns	18.5
15f	48.7	ns	24.5
15g	ns	19.0	ns
15h	40.0	ns	ns
15i	53.5	17.0	59.5
15l	42.9	35.0	ns
15m	49.5	ns	83.0
15n	23.32	29.5	ns
15o	27.5	31.0	ns
15p	46.0	16.5	ns
15q	16.5	ns	ns
Colchicine	84.7	84.8	79.0

Values are the mean of at least three independent determinations; coefficient of variation was less than 15%.
ns: not significant; % inhibition <10%.

they were much less potent than colchicine **4**. As shown in Table 2, this activity was more evident for L1210 cell line which resulted very sensitive towards styrylquinazolinones above all if they were unsubstituted at the 6 position (compounds **14**).

However, in spite of the lower activity of compounds **14** and **15** regarding colchicine **4**, a comparison with the antiproliferative activity of representative compounds **1b** and **1e** showed that the substitutions on the styryl moiety brought a moderate increase of the activity (Table 2).

4. Conclusion

In spite of the moderate antileukemic activity showed by compounds **14** and **15**, the results evidenced the positive role of the styryl moiety substitutions.

Starting from the most active compounds of the series, a study to investigate the influence of the 3-heterocyclic substitution on the antileukemic activity is in progress.

Table 2
IC_{50} recorded on K562, HL60 and L1210 cell lines of compounds **14a–c,e–m,o** and **15i,m**

	Compounds	IC_{50} (μM)
K562	**1b**	>2.75
	15i	1.65 ± 0.049
	Colchicine	<0.025
HL60	**14l**	2.33 ± 0.12
	Colchicine	<0.025
L1210	**1e**	>2.45
	14a	2.47 ± 0.011
	14b	1.99 ± 0.014
	14c	1.95 ± 0.014
	14e	1.94 ± 0.028
	14f	1.92 ± 0.040
	14g	2.04 ± 0.018
	14h	1.78 ± 0.056
	14i	1.92 ± 0.028
	14l	2.24 ± 0.014
	14m	2.32 ± 0.13
	14o	2.10 ± 0.098
	15i	1.77 ± 0.070
	15m	1.98 ± 0.035
	Colchicine	<0.025

5. Experimental section

5.1. Chemistry

All melting points were determined on a Büchi 530 capillary melting point apparatus and are uncorrected; IR spectra were recorded with a Jasco IR-810 spectrophotometer as nujol mull supported on NaCl disks; ^{1}H NMR spectra were obtained using a Bruker AC-E 250 MHz spectrometer (tetramethylsilane as internal standard). Microanalyses (C, H, N) performed in the laboratories of the Dipartimento di Scienze Farmaceutiche—Università di Catania, were within ±0.4% of the theoretical values.

*5.1.1. 6-Chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-methyl-4(3H)-quinazolinone **13***

Equimolar amount (0.015 mol) of 6-chloro-2-methylbenzooxazinone [14] **11** and 1-phenyl-3-methyl-5-aminopyrazole were heated at 160–180 °C for 2 h in oil bath. Upon cooling, the solid reaction material was crystallized from ethanol to give pure 6-chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-methyl-4(3H)-quinazolinone **13**; yields 46%.

Compound **13** is listed in Table 3.

*5.1.2. 3-(1-Phenyl-3-methylpyrazol-5-yl)-2-styryl-quinazolin-4(3H)-ones **14a–q** and 6-chloro-3-(1-phenyl-3-methylpyrazol-5-yl)-2-styrylquinazolin-4(3H)-ones **15b–q***

Equimolar amounts (10 mmol) of 6-*R*-3-(1-phenyl-3-methylpyrazol-5-yl)-2-methylquinazolinones **12** and **13** and the opportune benzoic aldehyde in acetic acid (10 ml) were reacted under reflux for 12 h.

The solid product, which separated, was filtered and crystallized from ethanol; in the case of compounds **14o,p** and

Table 3
Physical and spectroscopic data for compounds **13** and **14a–q**

Compounds	Melting point (°C) (a)	Formula	Yields (%)	IR (nujol) (cm^{-1})	^{1}H-NMR (b) (δ)
13	132	$C_{19}H_{15}N_4OCl$	37	1694 (CO)	2.17 (s, 3H, CH_3); 2.43 (s, 3H, CH_3); 6.32 (s, 1H, pyrazole H-4); 7.30–8.22 (a set of signals, 8H, aromatic protons)
14a	178–180	$C_{26}H_{20}N_4O$	87	1699 (CO)	2.48 (s, 3H, CH_3); 6.38 (s, 1H, pyrazole H-4); 6.43 (d, 1H, olefinic CH, J = 15.2 Hz); 7.21–8.27 (a set of signals, 15H, aromatic protons and olefinic CH)
14b	195	$C_{27}H_{22}N_4O_2$	52	1691 (CO)	2.15 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.37 (s, 1H, pyrazole H-4); 6.75 (d, 1H, olefinic CH, J = 15.5 Hz); 6.88–8.26 (a set of signals, 14H, aromatic protons and olefinic CH)
14c	131–134	$C_{27}H_{22}N_4O_2$	62	1692 (CO)	2.48 (s, 3H, CH_3); 3.82 (s, 3H, OCH_3); 6.39–6.44 (s + d, 2H, pyrazole H-4 and olefinic CH); 6.90–8.27 (a set of signals, 14H, aromatic protons and olefinic CH)
14d	178–180	$C_{27}H_{22}N_4O_2$	50	1680 (CO)	2.48 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.29 (d, 1H, olefinic CH, J = 15.2 Hz) 6.37 (s, 1H, pyrazole H-4); 6.87–8.25 (a set of signals, 14H, aromatic protons and olefinic CH)
14e	160	$C_{28}H_{24}N_4O_3$	56	1686 (CO)	2.47 (s, 3H, CH_3); 3.82 (s, 6H, 2XOCH_3); 6.37 (s, 1H, pyrazole H-4); 6.43–8.24 (a set of signals, 14H, aromatic protons and 2Xolefinic CH)
14f	163	$C_{28}H_{24}N_4O_3$	56	1692 (CO)	2.45 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 6.37 (s, 1H, pyrazole H-4); 6.70 (d, 1H, olefinic CH, J = 15.5 Hz); 6.94–8.27 (a set of signals, 13H, aromatic protons and olefinic CH)
14g	175	$C_{28}H_{24}N_4O_3$	65	1696 (CO)	2.47 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 6.26 (d, 1H, olefinic CH, J = 15.2 Hz); 6.38 (s, 1H, pyrazole H-4); 6.84–8.26 (a set of signals, 13H, aromatic protons and olefinic CH)
14h	156	$C_{29}H_{26}N_4O_4$	77	1690 (CO)	2.46 (s, 3H, CH_3); 3.87 (s, 6H, 2XOCH_3); 3.88 (s, 3H, OCH_3); 6.27 (d, 1H, olefinic CH, J = 15.6 Hz); 6.38 (s, 1H, pyrazole H-4); 6.61–8.27 (a set of signals, 12H, aromatic protons and olefinic CH)
14i	150	$C_{29}H_{26}N_4O_4$	59	1689 (CO)	2.46 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 6.37 (s, 1H, pyrazole H-4); 6.60–8.24 (a set of signals, 13H, aromatic protons and 2Xolefinic CH)
14l	163	$C_{26}H_{20}N_4O$	44	1693 (CO)	2.42 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 6.31–6.37 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.19–8.27 (a set of signals, 14H, aromatic protons and olefinic CH)
14m	160	$C_{26}H_{20}N_4O$	96	1688 (CO)	2.36 (s, 3H, CH_3); 2.47 (s, 3H, CH_3); 6.37 (s, 1H, pyrazole H-4); 6.42 (d, 1H, olefinic CH, J = 15.5 Hz); 7.20–8.25 (a set of signals, 14H, aromatic protons and olefinic CH)
14n	170	$C_{26}H_{20}N_4O$	95	1681 (CO)	2.37 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 6.35–6.42 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.16–8.25 (a set of signals, 14H, aromatic protons and olefinic CH)
14o	222	$C_{26}H_{19}N_5O_2$	65	1684 (CO)	2.43 (s, 3H, CH_3); 6.35–6.41; (s + d, 2H, pyrazole H-4 and olefinic CH); 7.26–8.32 (a set of signals, 14H, aromatic protons and olefinic CH)
14p	204	$C_{26}H_{19}N_4O_3Cl$	64	1681 (CO)	2.48 (s, 3H, CH_3); 6.36–6.42 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.23–8.24 (a set of signals, 14H, aromatic protons and olefinic CH)
14q	191	$C_{28}H_{24}N_4O_3$	34	1672 (CO)	2.41 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 6.13 (d, 1H, olefinic CH, J = 14.4 Hz); 6.65 (s, 1H, pyrazole H-4); 6.89–8.12 (a set of signals, 13H, aromatic protons and olefinic CH); 9.40 (br s, 1H, exchangeable OH)

(a) Ethanol for compounds **14a–n**; dioxane for compounds **14o–p**.
(b) $CDCl_3$.

15d,e,g,m–q the solid was crystallized from dioxane. Yield 22–96%.

Compounds **14a–q** and **15b–q** are listed in Tables 3 and 4, respectively.

5.2. Biology

5.2.1. Antiproliferative activity in vitro

Compounds **14a–q** and **15b–q** were tested in vitro for antileukemic activity against L1210 (murine leukemia), K562 (human chronic myelogenous leukemia) and HL60 (human leukemia) cell lines. These cell lines were grown at 37 °C in a humidified atmosphere containing 5% CO_2, in RPMI-1640 medium (Biochrom KG) supplemented with 10% fetal calf serum and antibiotics.

L1210 and K562 were suspended at a density of 1×10^5 or 2×10^5 in the case of HL60, cells per ml in growth medium, transferred to 24-well plate (1 ml per well), cultured with or without screening concentration of compounds and incubated at 37 °C for 48 h.

Numbers of viable cells were determined by counting in a hematocytometer after dye exclusion with trypan blue [18]. We determined IC_{50} values (test agent concentration at which the cell proliferation was inhibited to 50% of the untreated growth control) for compounds that exhibited the best activity at screening concentration.

Acknowledgements

Financial support from MIUR is gratefully acknowledged.

Table 4
Physical and spectroscopic data for compounds **15b–q**

Compounds	Melting point (°C) (a)	Formula	Yields (%)	IR (nujol) (cm^{-1})	^{1}H-NMR (b) (δ)
15b	181–183	$C_{27}H_{21}N_4O_2Cl$	66	1679 (CO)	2.48 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.39 (s, 1H, pyrazole H-4); 6.75 (d, 1H, olefinic CH, J = 15.3 Hz); 6.92–8.20 (a set of signals, 13H, aromatic protons and olefinic CH)
15c	215–217	$C_{27}H_{21}N_4O_2Cl$	73	1694 (CO)	2.47 (s, 3H, CH_3); 3.82 (s, 3H, OCH_3); 6.36–6.43 (s + d, 2H, pyrazole H-4 and olefinic CH); 6.91–8.20 (a set of signals, 13H, aromatic protons and olefinic CH)
15d	204	$C_{27}H_{21}N_4O_2Cl$	81	1693 (CO)	2.48 (s, 3H, CH_3); 3.82 (s, 3H, OCH_3); 6.27 (d, 1H, olefinic CH, J = 15.2 Hz); 6.39 (s, 1H, pyrazole H-4); 6.87–8.17 (a set of signals, 13H, aromatic protons and olefinic CH)
15e	220	$C_{28}H_{23}N_4O_3Cl$	63	1692 (CO)	2.48 (s, 3H, CH_3); 3.81 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.38 (s, 1H, pyrazole H-4); 6.42–8.16 (a set of signals, 13H, aromatic protons and 2Xolefinic CH)
15f	110	$C_{28}H_{23}N_4O_3Cl$	78	1688(CO)	2.45 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 6.37 (s, 1H, pyrazole H-4); 6.67 (d, 1H, olefinic CH, J = 15.4 Hz); 6.65–8.17 (a set of signals, 12H, aromatic protons and olefinic CH)
15g	148–150	$C_{28}H_{23}N_4O_3Cl$	80	1687 (CO)	2.47 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 6.26 (d, 1H, olefinic CH, J = 15.2 Hz); 6.40 (s, 1H, pyrazole H-4); 6.86–8.18 (a set of signals, 12H, aromatic protons and olefinic CH)
15h	191	$C_{29}H_{25}N_4O_4Cl$	56	1687 (CO)	2.46 (s, 3H, CH_3); 3.87 (s, 6H, $2XOCH_3$); 3.88 (s, 3H, OCH3); 6.24 (d, 1H, olefinic CH, J = 15.3 Hz); 6.39 (s, 1H, pyrazole H-4); 6.60–8.20 (a set of signals, 11H, aromatic protons and olefinic CH)
15i	150	$C_{29}H_{25}N_4O_4Cl$	68	1692 (CO)	2.46 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 6.37 (s, 1H, pyrazole H-4); 6.62 (d, 1H, olefinic CH, J = 15.2 Hz); 6.68–8.18 (a set of signals, 11H, aromatic protons and olefinic CH)
15l	168	$C_{26}H_{19}N_4OCl$	22	1699 (CO)	2.43 (s, 3H, CH_3); 2.46 (s, 3H, CH_3); 6.33 (d, 1H, olefinic CH, J = 15.2 Hz); 6.37 (s, 1H, pyrazole H-4); 7.19–8.20 (a set of signals, 13H, aromatic protons and olefinic CH)
15m	196	$C_{26}H_{19}N_4OCl$	40	1704 (CO)	2.36 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 6.39–6.45 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.20–8.19 (a set of signals, 13H, aromatic protons and olefinic CH)
15n	220	$C_{26}H_{19}N_4OCl$	56	1698 (CO)	2.37 (s, 3H, CH_3); 2.48 (s, 3H, CH_3); 6.35–6.40 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.16–8.18 (a set of signals, 13H, aromatic protons and olefinic CH)
15o	228	$C_{26}H_{18}N_5O_2Cl$	65	1693 (CO)	2.44 (s, 3H, CH_3); 6.34–6.40 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.29–8.33 (a set of signals, 13H, aromatic protons and olefinic CH)
15p	230	$C_{26}H_{18}N_4O_3Cl$	42	1682 (CO)	2.48 (s, 3H, CH_3); 6.34–6.39 (s + d, 2H, pyrazole H-4 and olefinic CH); 7.23–8.20 (a set of signals, 13H, aromatic protons and olefinic CH)
15q	204	$C_{28}H_{23}N_4O_3Cl$	78	1690 (CO)	2.49 (s, 3H, CH_3); 3.93 (s, 3H, OCH_3); 6.27 (d, 1H, olefinic CH, J = 15.4 Hz); 6.39 (s, 1H, pyrazole H-4); 6.81–8.18 (a set of signals, 12H, aromatic protons and olefinic CH); the OH signal is indetectable

(a) Ethanol for compounds **15b,c,f,h–l**; dioxane for compounds **15d,e,g,m–q**.
(b) $CDCl_3$ for compounds **14a–p**; DMSO-d_6 for compound **15q**.

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