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Nucleophilic substitutions in the isoindole series as a valuable tool to synthesize derivatives with antitumor activity

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ABSTRACT

A novel synthetic approach to the synthesis of 3-substituted isoindoles through nucleophilic substitution of 3-halo derivatives by charged carbon, and neutral nitrogen, oxygen, and sulfur nucleophiles, assisted by a 1-acyl group, is reported. Aryl-thio-isoindoles, obtained through a direct nucleophilic substitution with sulfur nucleophiles, showed cytotoxic activity, with GI_{50} values from micromolar to sub-micromolar concentrations, against the total number of cell lines investigated.

1. Introduction

Isoindoles appeared late on the chemical scene. Early attempts to prepare isoindole or its simple derivatives were unsuccessful and these compounds did not become known until 1951 when Wittig obtained 2-methylisoindole.[1] Isoindoles are very unstable and easily undergo autoxidation and self-condensation reactions. However, *N*-substituted isoindoles are generally more stable than *N*-unsubstituted compounds.

The chemistry of isoindoles is characterized by their strong tendency to undergo ready electrophilic substitution at the five-membered ring, due to their high π-electron density, preferentially at the C-1 (C-3) position.[1] On the contrary, very few examples of nucleophilic reactions in the isoindole series have been reported.

In fact, direct nucleophilic substitution in the isoindole series involved replacement of an ethoxy group, bound to the position 1 of an isoindolenine structure, by primary aromatic amines, heterocyclic amines, benzylamines, hydrazines, and hydroxylamines.[2] The sole example of halogen replacement from an isoindole system was observed, only very recently, in the case of the reaction of 1,1,3-trichloro-1*H*-isoindole with hydrazines to give 1,3-disubstituted 1*H*-isoindoles.[3]

We have reported direct aromatic nucleophilic substitutions on halogenated pyrroles[4] and more recently on indoles;[5] such reactions proved to be good methods to functionalize these π-excessive heterocycles.

Thus, considering our interest in the isoindole system, and hoping to get a useful tool to introduce a variety of functional groups into the isoindole moiety, we decided to perform nucleophilic substitutions on 3-haloisoindoles, bearing suitable substituents on position 1, and, if possible, to compare their reactivity with those of the pyrrole and indole ring systems.

This study was further encouraged by the interesting antitumor activity of several compounds containing the isoindole moiety,[6–11] and by the potent antiproliferative activity of arylthioindoles.[12]

In this paper we describe the reactivity of 3-halo-2*H*-isoindoles toward charged carbon, and neutral nitrogen, oxygen, and sulfur nucleophiles. We also report the antitumor activity of arylthioisoindoles obtained through a direct nucleophilic substitution with sulfur nucleophiles.

2. Results and discussions

2.1. Chemistry

We selected 3-halo-2*H*-isoindoles **5**–**8** as substrates to perform nucleophilic substitutions. Such compounds were synthesized according to the synthesis reported for derivatives **5** and **7**.[13] Thus,

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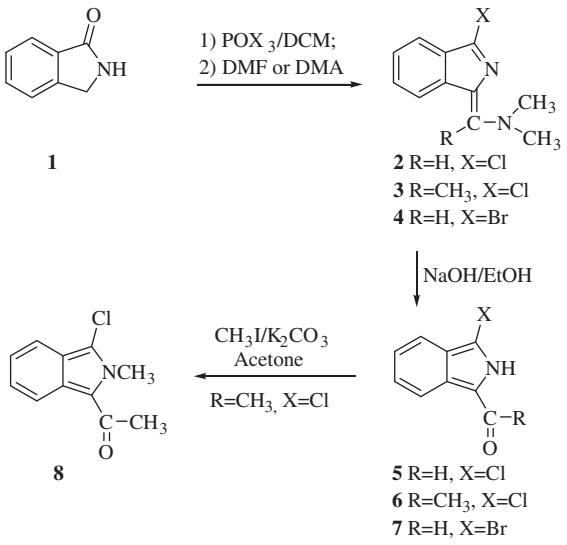
treatment of phthalimidine **1** with 2 M equivalents of the Vilsmeier reagent, obtained by reaction of POX_3 (X=Cl, Br) with dimethylformamide (DMF) or dimethylacetamide (DMA), gave the isoindolenine derivatives **2**–**4** (55–91%) as shown Scheme 1.



Scheme 1. Synthesis of 3-halo-2*H*-isoindoles **5**–**8**.

Basic hydrolysis of the latter furnished the isoindoles **5**–**7** in good yields (74–86%). 1-Acetyl-3-chloro-2*H*-isoindole **6** was converted into the corresponding *N*-methyl derivative **8** using potassium carbonate and methyl iodide in anhydrous acetone (50%) (Scheme 1).

Our first attempts at nucleophilic reactions, were carried out by heating under reflux a mixture of halo-isoindoles in DMF, an excess of the nucleophile and, in the case of arylthioles, phenols, and amines, a stoichiometric amount of triethylamine (TEA) in order to neutralize the halogenidric acid formed (Method A).

Thus, under such conditions, 3-chloro-isoindoles **5** and **6** reacted with arylthioles to afford compounds **9**–**16** in good yields (52–80%). When the same sulfur nucleophiles were reacted with 3-bromo-isoindole **7**, the corresponding direct substitution products **9**–**12** were obtained in poor yields (10–25%). Instead, surprisingly, the *N*-substituted 3-chloro-isoindole **8** did not provide the nucleophilic substitution products (Scheme 2 and Table 1).

When 3-halo-isoindoles **7** and **8** were reacted with sulfur nucleophiles, using ethanol as solvent and a stoichiometric amount of TEA (Method B), the direct nucleophilic substitution products **9**–**12** and **17**–**20**, respectively, were obtained in good to excellent yields (57–99%).

Moreover, 1-carboxaldehyde-3-halo-isoindoles **5** and **7** reacted with an excess of arylthioles and a stoichiometric amount of TEA under microwave irradiation (Method C) to afford compounds **9**–**12** in higher yield (65–85%) in a much shorter time (5 min). Surprisingly, when 1-acetyl-3-chloro-isoindole **6** was reacted under the same reaction conditions (Method C), derivatives **13**–**16** were obtained in lower yields (30–37%) (Table 1).

Reaction of 1-carboxaldehyde-3-chloro-isoindole **5** with substituted amines (Method A), gave compounds **21**–**25** in good yields (50–70%). Conduction of the reaction under microwave irradiation did not lead to any improvement providing the substitution products **21**–**25** in 55–71% (Method C). Whereas when ethanol was used as solvent (Method B), only products **21** and **22** were isolated (89 and 64% yields, respectively).

1-Acetyl-3-chloro-isoindole **6** only reacted with benzylamine and pyrrolidine in ethanol, (Method B), to give the nucleophilic substitution products **26** and **27**, respectively, in low yields (9–33%).

Instead, from the reaction of 3-bromo-1-carboxaldehyde-isoindole **7** and amines it was possible to isolate the direct nucleophilic substitution products **21**–**25** (Method B) in excellent yields (80–100%).

1-Acetyl-3-chloro-2-methyl-isoindole **8** provided the nucleophilic substitution product **28**, in moderate yield (41%), only when the nucleophile pyrrolidine was used as a solvent (Method D).

Reaction of 3-halo-isoindoles **5** and **7** with 4-methoxyphenol furnished the 1-carboxaldehyde-3-(4-methoxyphenoxy)-2*H*-isoindole **29** in poor yields, 8% (Method A) and 15% (Method C), respectively. The same direct nucleophilic product was obtained from the same halo-isoindoles, under microwave irradiation (Method C), in 35 and 42% yields, respectively.

Nucleophilic reactions of 3-halo-isoindoles **5** and **7** with charged nucleophiles (malononitrile and ethyl cyanoacetate salts and NaCN), in DMF as a solvent (Method A), did not provide the nucleophilic substitution products probably because of the poor solubility of the nucleophiles in the reaction solvent. Instead 1-acetyl-3-chloro-2-methyl-isoindole **8** furnished the substitution product **33**, in good yield (70%) when NaCN was used as nucleophile. When substrates **5** and **7** were reacted with malononitrile and ethyl cyanoacetate salts in ethanol (Method B), the substitution products **30** and **31** were obtained in 40–51% yields. The same reactions carried out under microwave irradiation (Method C) gave compounds **30** and **31** with mixed results. In the attempt to improve the yields of these compounds, and considering that in the indole series the best results in the nucleophilic substitution reactions were obtained under phase transfer catalysis, substrate **5** was reacted by heating at 60 °C a mixture of an excess of the above mentioned nucleophile and 18-crown-6 as phase transfer catalyst (Method E). This method gave derivatives **30** and **31** in lower yields (15%).

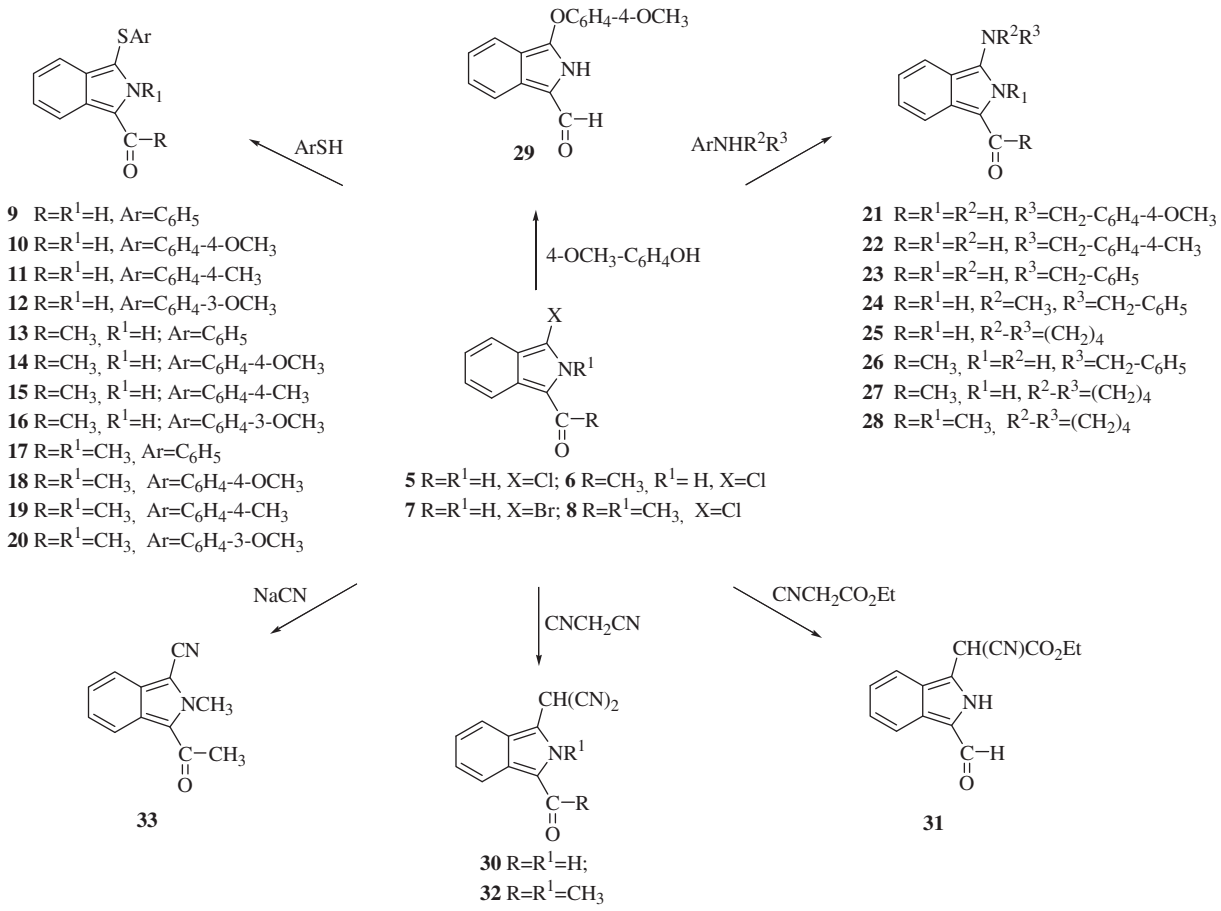
Reaction of 1-acetyl-2-methyl-3-chloro-isoindole **8** with malononitrile gave the substitution product **32** in moderate yields (30%) (Method B). The yield of this compound did not improve by using methods C (20%) and E (16%).

Thus, as in the case of pyrroles and indoles, isoindoles can also be functionalized through nucleophilic replacement of halogens assisted by a 1-acyl group. However, although some reactions did not fulfill these expectations, probably due to the instability of the products under the reaction conditions, it is possible to outline some reactivity features of the isoindole system. Chloro derivatives reacted well in an aprotic dipolar solvent (DMF), whereas the bromo derivatives gave best results in ethanol, a highly solvating solvent. In contrast with the pyrrole series, in which nucleophilic substitutions take place only on the *N*-methyl derivatives, isoindoles resemble the indoles in which *N*-unsubstituted derivatives are more reactive than the corresponding *N*-methyl compounds. In contrast to halo-indoles, which did not react with charged carbon nucleophiles, replacement of halogen by cyanide and methylene active compounds was observed in isoindole series.

2.2. Anticancer activity

The potent antitumor activity showed by arylthioindoles encouraged us to evaluate the aryl-thio-isoindoles **9**–**20** for such a biological property. Arylthioindoles are potent tubulin assembly inhibitors and bind the colchicine site. They show antitumor activity comparable with those of colchicines and combretastatin A-4.[12]

All of the isolated aryl-thio-isoindoles **9**–**20** were submitted to the National Cancer Institute (Bethesda MD) and five of them (**9**,**10**, **13**, **14**, and **17**) were pre-screened, at one dose concentration (10^{-5} M), in a panel of approximately 60 tumor cell lines that have grouped in disease sub-panels including leukemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumors cell lines.



Scheme 2. Reactivity of 1-halo-2*H*-isoindoles **5**–**8** toward charged carbon, and neutral nitrogen, oxygen, and sulfur nucleophiles.

Compounds **10** and **14** were further selected for full evaluation at five concentration levels (10^{-4}–10^{-8} M).

The antitumor activity of compounds was given by three parameters for each cell line; pGI_{50} value (GI_{50} is the molar concentration of the compound that inhibits 50% net cell growth), pTGI value (TGI is the molar concentration of the compound leading to total inhibition of net cell growth), and pLC_{50} value (LC_{50} is the molar concentration of the compound that induces 50% net cell death). An evaluation of the data reported in the Tables 2 and 3 revealed that compounds **10**,**14** were cytotoxic showing GI_{50} values against the total number of cell lines investigated from micromolar to sub-micromolar concentrations.

Moreover, positive TGI (98–100%) and LC_{50} (63–75%) values were observed with respect to a good number of cell lines. In particular aryl-thio-isoindoles **10**,**14** were selective with respect to the colon, renal, and leukemia sub-panels.

The most sensitive cell lines resulted COLO 205 (pGI_{50} 6.76 and 6.18, respectively) of colon cancer sub-panel, A498 (pGI_{50} 6.58 and 5.46, respectively) of renal cancer sub-panel, and SR (pGI_{50} 5.87 and 5.78, respectively) of leukemia sub-panel (Table 3). Derivative **10** also showed selectivity with respect to MOLT-4, (pGI_{50} 5.88) of leukemia sub-panel, and MDA-MB-468 (pGI_{50} 5.85) of breast cancer sub-panel (Table 3).

2.3. Docking

Microtubules are a component of the mitotic spindle, and they are essential for many cellular processes. Compounds that are able to interfere with the microtubule equilibrium in cells are useful in the treatment of human diseases.[14,15] Most of the antimitotic drugs in clinical use bind at the three major binding sites of tubulin: the vinca, taxane, and colchicine sites.[16] Combretastatin A-4 (CA-4) strongly inhibits the tubulin assembly by binding to the colchicines site and prevents tubulin polymerization.[17]

Docking studies were performed to investigate the binding ability of the aryl-thio-isoindoles to the colchicines binding site.

Isoindole **14** was docked inside the colchicine binding site of tubulin (PBD code 1SA0),[18] using GLIDE software XP mode default parameters.[19] To validate the use of GLIDE, the docking studies were performed on the reference compounds DAMA–colchicine and combretastatin A-4 (CA-4). Such studies showed that compound **14** overlaps well with the CA-4 in the crystallized protein complex. Derivative **14** established hydrogen bond between the C-3 acetyl moiety of isoindole ring and Ser 178, the C-4 methoxy group of phenyl ring is in close proximity to Cys 241, a key residue for the binding and biological activity of many colchicine analogues.[13]

Hydrophobic contacts (Ala 180, Leu 255 and Leu 248) stabilize the binding of the isoindole **14** to the protein (Figs. 1 and 2).

It is our intention to carry out biological studies in order to verify if the aryl-thio-isoindoles act as antimitotic agents.

3. Experimental section

3.1. General

All melting points were taken on a Büchi–Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C NMR

Table 1
Direct nucleophilic substitution products of 1-substituted-3-halo-isoindoles

Substrate	Nucleophile	Product	Method (%Yield)				
			A	B	C	D	E
5	HS–C_6H_5	**9**	52	—	81	—	—
7	HS–C_6H_5	**9**	10	66	85	—	—
5	HS–C_6H_4-4–OMe	**10**	73	—	80	—	—
7	HS–C_6H_4-4–OMe	**10**	19	57	70	—	—
5	HS–C_6H_4-4–Me	**11**	63	—	65	—	—
7	HS–C_6H_4-4–Me	**11**	25	75	82	—	—
5	HS–C_6H_4-3–OMe	**12**	60	—	75	—	—
7	HS–C_6H_4-3–OMe	**12**	13	67	78	—	—
6	HS–C_6H_5	**13**	53	—	30	—	—
6	HS–C_6H_4-4–OMe	**14**	72	—	31	—	—
6	HS–C_6H_4-4–Me	**15**	72	—	37	—	—
6	HS–C_6H_4-3–OMe	**16**	80	—	36	—	—
8	HS–C_6H_5	**17**	0	99	—	—	—
8	HS–C_6H_4-4–OMe	**18**	0	70	—	—	—
8	HS–C_6H_4-4–Me	**19**	0	98	—	—	—
8	HS–C_6H_4-3–OMe	**20**	0	80	—	—	—
5	H_2N–CH_2–C_6H_4-4-OMe	**21**	60	89	66	—	—
7	H_2N–CH_2–C_6H_4–4-OMe	**21**	0	100	—	—	—
5	H_2N–CH_2–C_6H_4-4–Me	**22**	60	64	55	—	—
7	H_2N–CH_2–C_6H_4-4–Me	**22**	0	98	—	—	—
5	H_2N–CH_2–C_6H_5	**23**	53	0	50	—	—
7	H_2N–CH_2–C_6H_5	**23**	0	96	—	—	—
5	H_2N–(CH_3)–CH_2–C_6H_5	**24**	50	0	51	—	—
7	H_2N–(CH_3)–CH_2–C_6H_5	**24**	0	80	—	—	—
5	Pyrrolidine	**25**	70	0	71	—	—
7	Pyrrolidine	**25**	0	99	—	—	—
6	H_2N–CH_2–C_6H_5	**26**	0	9	—	—	—
6	Pyrrolidine	**27**	0	33	—	—	—
8	Pyrrolidine	**28**	0	0	0	41	—
5	HO–C_6H_4-4–OMe	**29**	8	—	35	—	—
7	HO–C_6H_4-4–OMe	**29**	0	15	42	—	—
5	CN–CH_2–CN	**30**	0	40	70	—	15
7	CN–CH_2–CN	**30**	0	51	40	—	—
5	CN–CH_2–CO_2Et	**31**	0	40	20	—	15
7	CN–CH_2–CO_2Et	**31**	0	40	30	—	—
8	CN–CH_2–CN	**32**	0	30	28	—	16
8	NaCN	**33**	70	—	—	—	—

Methods: A (Nu/DMF and TEA in the cases of thiols, 4-methoxyphenol and amines, reflux, 0.5–2 h), B (Nu/EtOH and TEA in the cases of thiols, 4-methoxyphenol and amines, 50 °C, 6–23 h), C (Nu/DMF and TEA in the cases of thiols, 4-methoxyphenol and amines, 150 W, 150 °C, 5 min), D (Nu, reflux, 30 h), E (Nu/KOH/18-crown-6 ether/CH_3CN, 60 °C, 8–10 h).

Table 2
Overview of the results of the in vitro antitumor screening for compounds **10** and **14**[a]

10	No.[e]	*N*[f]	Range	MG_MID[g]
pGI_{50}[b]	60	60	4.65–6.18	5.13
pTGI[c]	60	59	4.08–5.22	4.58
pLC_{50}[d]	60	38	4.01–4.57	4.15
14	No.	*N*	Range	MG_MID
pGI_{50}	60	60	4.75–6.76	5.08
pTGI	60	60	4.27–6.40	4.60
pLC_{50}	60	45	4.01–6.04	4.18

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen.
[b] pGI_{50} is the −log of the molar concentration that inhibits 50% net cell growth.
[c] pTGI is the −log of the molar concentration giving total growth inhibition.
[d] pLC_{50} is the −log of the molar concentration leading to 50% net cell death.
[e] No. is the number of the cell lines investigated.
[f] *N* is the number of cell lines giving positive pGI_{50}, pTGI, and pLC_{50}.
[g] MG_MID=mean graph midpoint=arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

spectra were measured at 200 and 50.3 MHz, respectively, in DMSO-d_6 or $CDCl_3$ solution, using a Bruker Avance II series 200 MHz spectrometer (TMS as internal reference). Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with Büchi Sepacore chromatography module (prepacked cartridge system). Elemental analyses (C, H, N) were performed with a VARIO EL

Table 3
Inhibition of in vitro cancer cell lines by compounds **10** and **14**[a]

Cell line	pGI_{50}[a]	
	10	**14**
Leukemia		
CCRF-CEM	5.25	4.84
HL-60(TB)	5.29	4.82
K-562	5.67	5.58
MOLT-4	5.88	
RPMI-8226	5.15	4.96
SR	5.78	5.87
Non-small cell lung cancer		
A549/ATCC	4.88	5.40
EKVX	5.26	5.09
HOP-62	4.81	4.90
HOP-92	5.26	5.62
NCI-H226	5.58	5.25
NCI-H23	4.85	4.83
NCI-322M	5.09	4.88
NCI-H460	5.53	5.13
NCI-H522	4.85	4.99
Colon cancer		
COLO 205	6.18	6.76
HCC-2998	5.26	4.92
HCT-116	4.90	4.92
HCT-15	4.94	4.94
HT29	5.40	4.81
KM12	5.44	5.19
SW-620	5.43	4.90
CNC cancer		
SF-268	4.83	4.89
SF-295	5.04	4.94
SF-539	4.96	4.84
SNB-19	5.32	4.94
SNB-75	4.92	4.97
U251	4.91	4.92
Melanoma		
LOX IMVI	4.91	4.93
MALME-3M	4.85	4.75
M14	4.91	4.93
MDA-MB-435	5.57	5.56
SK-MEL-2	4.87	4.89
SK-MEL-28	4.82	4.87
SK-MEL-5	4.89	4.90
UACC-257	4.70	4.82
UACC-62	4.96	4.99
Ovarian cancer		
IGROV1	4.86	4.93
OVCAR-3	4.93	4.91
OVCAR-4	4.65	4.88
OVCAR-5	5.22	4.76
OVCAR-8	4.85	4.78
NCI/ADR-RES	4.94	4.93
SK-OV-3	5.30	5.75
Renal cancer		
786–0	4.92	4.78
A498	5.46	6.58
ACHN	4.83	4.78
CAKI-1	4.78	5.54
RXF 393	4.97	4.87
SN12C	4.83	4.96
TK-10	4.97	4.82
UO-31	5.29	5.23
Prostate cancer		
PC-3	4.88	4.95
DU-145	5.20	4.80
Breast cancer		
MCF7	4.89	4.91

(*continued on next page*)

Table 3 (*continued*)

Cell line	pGI_{50}[a]	
	10	**14**
MDA-MB-231/ATCC	4.87	4.94
HS 578T	5.19	4.96
BT-549	5.69	5.50
T-47D	5.04	5.08
MDA-MB-468	5.85	5.41

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen.

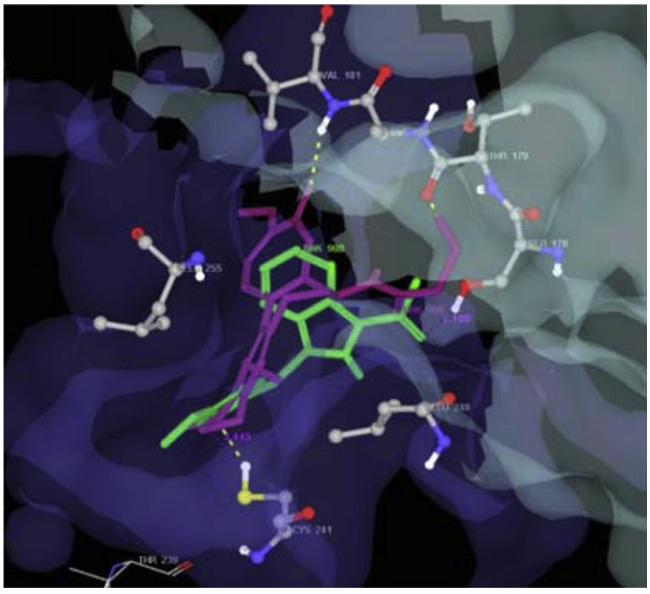


Fig. 1. The structure of **14** (green) and DAMA–colchicine (purple) docked into the colchicines binding site of tubulin.

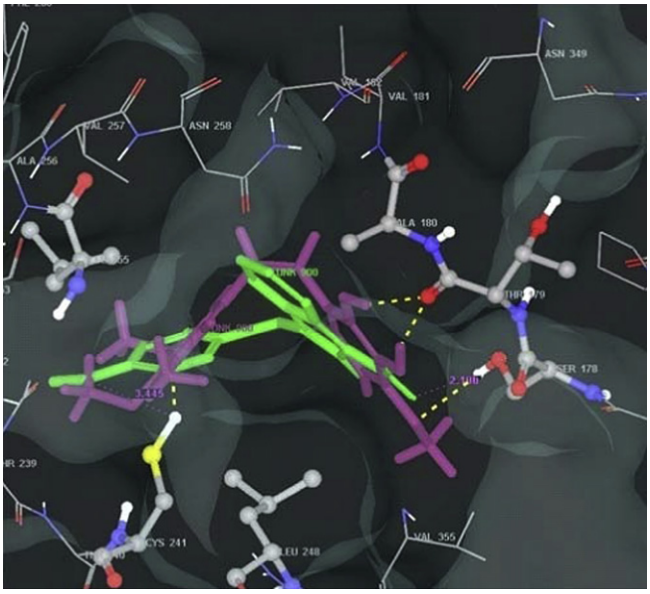


Fig. 2. The structure of **14** (green) and **CA-4** (purple) docked into the colchicines binding site of tubulin.

III elemental analyzers. Microwave experiments were carried out using a CEM Discover LabmateTM microwave apparatus.

Elemental analyses were within 0.4% of the theoretical values and were performed with a VARIO EL III elemental analyzer.

*3.1.1. 2,3-Dihydro-1H-isoindol-1-one (**1**).* This compound was prepared from phthalimide according to the procedure of von Dobeneck et al.[13] Yield 80%. Mp 150–151 °C (lit. mp 148–150 °C).

*3.1.2. 1-(3-Halo-1H-isoindol-1-ylidene)-N,N-dialkylmethan amine (**2**–**4**).* A solution of $POCl_3$ or $POBr_3$ (30 mmol) in anhydrous DCM (7 mL) was added dropwise to DMF or DMA (30 mmol) in anhydrous DCM (15 mL) at 0 °C. The mixture was stirred for 30 min at room temperature. Then, a solution of 1*H*-isoindolinone **1** (2 g, 15 mmol) in anhydrous DCM (75 mL) was added to the mixture, at 0 °C. Subsequently, the reaction mixture was heated at reflux for 5 h, and then after cooling, the solvent was removed at reduced pressure. Ice-water was added, and the mixture was neutralized with NaOH 5 M. The precipitate was filtered out, washed with water and dried. The residue was recrystallized from MeOH/H_2O (1:1) to give the following compounds.

*3.1.3. 1-(3-Chloro-1H-isoindol-1-ylidene)-N,N-dimethyl methanam ine (**2**).* Yield (2.29 g, 74%) as cream solid, mp 108–110 °C. IR: 1635 (CN) cm^{-1}. ^1H NMR $CDCl_3$: δ 3.46 (br s, 6H, 2×CH_3), 7.15 (s, 1H, CH), 7.23 (t, *J*=8.2 Hz, 1H, H-5), 7.29 (t, *J*=8.2 Hz, 1H, H-6), 7.56 (d, *J*=8.2 Hz, 1H, H-4), 7.61 (d, *J*=8.2 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 41.2 (q) 46.7 (q), 116.0 (d), 119.6 (d), 122.2 (s), 122.9 (d), 126.0 (d), 129.9 (s), 138.7(d), 140.9 (s), 142.9 (s). Anal. Calcd for $C_{11}H_{11}ClN_2$: C, 65.93; H, 5.36; N, 13.55. Found: C, 65.76; H, 5.60; N, 13.49.

*3.1.4. 1-(3-Chloro-1H-isoindol-1-ylidene)-N,N-dimethyl ethanamine (**3**).* Yield (1.82 g, 55%) as cream solid, mp 110–112 °C. IR: 1566 (CN) cm^{-1}. ^1H NMR DMSO-d_6: δ 2.69 (s, 3H, CH_3), 3.49 (br s, 6H, 2×CH_3), 7.15 (t, *J*=8.0 Hz, 1H, H-5), 7.29 (t, *J*=8.0 Hz, 1H, H-6), 7.51 (d, *J*=8.0 Hz, 1H, H-4), 7.83 (d, *J*=8.0 Hz, 1H, H-7). ^{13}C NMR DMSO-d_6: δ 19.4 (q), 44.1 (q×2), 113.7 (s), 118.6 (d), 120.4 (d), 121.4 (d), 122.5 (s), 125.2 (d), 129.2 (s), 137.5 (s), 156.4 (s). Anal. Calcd for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; N, 10.52. Found: C, 65.22; H, 6.03; N 10.27.

*3.1.5. 1-(3-Bromo-1H-isoindol-1-ylidene)-N,N-dimethyl methanam ine (**4**).* Yield (3.43 g, 91%) as cream solid, mp 136–137 °C. IR: 1635 (CN) cm^{-1}. ^1H NMR DMSO-d_6: δ 3.35 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 7.17 (t, *J*=7.8 Hz, 1H, H-5), 7.30 (t, *J*=7.8 Hz, 1H, H-6), 7.44 (d, *J*=7.8 Hz, 1H, H-4), 7.86 (d, *J*=7.8 Hz, 1H, H-7), 7.93 (s, 1H, CH). ^{13}C NMR DMSO-d_6: δ 40.1 (q), 46.2 (q) 116.6 (d), 119.0 (d), 122.3 (d), 122.9 (s), 125.3 (d), 128.8 (s), 130.6 (s), 140.2 (s), 141.6 (d). Anal. Calcd for $C_{11}H_{11}BrN_2$: C, 52.61; H, 4.42; N, 11.16. Found: C, 52.44; H, 4.71; N, 11.01.

3.2. General procedure for the preparation of 1-substituted-3-halo-2*H*-isoindoles (5–7)

A solution of proper 3-halo-isoindolylidene **2**–**4** (5 mmol), NaOH (4 M, 5 mL), and ethanol (65 mL) was heated at reflux for 3 h. After cooling, the solvent was evaporated at reduced pressure and the reaction residue was neutralized with HCl (3 M). The resulting precipitated was filtered off, washed with water, and dried over P_2O_5. The crude residue was recrystallized from MeOH/H_2O (1:3) to give the following compounds.

*3.2.1. 1-Carboxaldehyde-3-chloro-2H-isoindole (**5**).* Yield (0.77 g, 86%) as white solid, mp 126–127 °C. IR: 3436 (NH), 1606 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 7.25 (t, *J*=7.7 Hz, 1H, H-5), 7.41 (t, *J*=7.7 Hz, 1H, H-6), 7.65 (d, *J*=7.7 Hz, 1H, H-4), 8.13 (d, *J*=7.7 Hz, 1H, H-7), 9.82 (br s, 1H, CHO), 14.30 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 118.3 (s), 118.9 (s), 119.0 (d×2), 121.2 (s), 122.4 (s), 123.6 (d), 127.3 (d), 174.1 (d). Anal. Calcd for C_9H_6ClNO: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.48; H, 3.13; N, 7.62.

*3.2.2. 1-Acetyl-3-chloro-2H-isoindole (**6**).* Yield (0.72 g, 74%) as white solid, mp 159–160 °C. IR: 3320 (NH), 1624 (CO) cm^{-1}. ^1H NMR

DMSO-d_6: δ 2.57 (s, 3H, CH_3) 7.18 (t, J=8.7 Hz, 1H, H-5), 7.35 (t, J=8.7 Hz, 1H, H-6), 7.61 (d, J=8.7 Hz, 1H, H-4), 8.07 (d, J=8.7 Hz, 1H, H-7), 13.90 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 27.5 (q), 113.8 (s×2) 118.8 (d), 120.5 (s), 120.6 (d), 122.0 (s), 122.7 (d), 126.7 (d), 184.2 (s). Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.38; H, 4.31; N, 7.41.

*3.2.3. 3-Bromo-1-carboxaldehyde-2H-isoindole (**7**).* Yield (0.94 g, 84%) as white solid, mp 110–111 °C. IR: 3077 (NH), 1600 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 7.25 (t, J=7.8 Hz, 1H, H-5), 7.39 (t, J=7.8 Hz, 1H, H-6), 7.57 (d, J=7.8 Hz, 1H, H-4), 8.13 (d, J=7.8 Hz, 1H, H-7), 9.82 (br s, 1H, CHO), 13.77 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 118.1 (s), 118.6 (s), 119.0 (s), 119.7 (d), 123.6 (d×2), 125.1 (s), 127.0 (d), 174.3 (d). Anal. Calcd for C_9H_6BrNO: C, 48.25; H, 2.70; N, 6.25. Found: C, 48.55; H, 2.43; N, 6.01.

*3.2.4. 1-Acetyl-3-chloro-2-methyl-2H-isoindole (**8**).* A solution of 1-acetyl-3-chloro-2*H*-isoindole **6** (1.16 g, 6 mmol) in anhydrous acetone (30 mL) was treated with finely powdered anhydrous K_2CO_3 (1.12 g, 8.16 mmol). The resulting suspension was stirred vigorously for 4 h under nitrogen atmosphere. Iodomethane (1.02 mL, 16.32 mmol) was then added, and stirring was continued for 16 h. The suspension was filtered off and the crude solid washed with acetone (3×10 mL). The filtrate was evaporated to a solid residue that was stirred in 25 mL of H_2O. The solid was collected by filtration, dried over P_2O_5, and purified by column chromatography, eluting with dichloromethane, to give the *title compound* **8** (0.62 g, 50%) as white solid.

Mp 93–94 °C. IR: 1622 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 2.69 (s, 3H, CH_3), 4.24 (s, 3H, CH_3), 7.14 (t, J=8.7 Hz, 1H, H-5), 7.32 (t, J=8.7 Hz, 1H, H-6), 7.61 (d, J=8.7 Hz, 1H, H-4), 7.81 (d, J=8.7 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 30.6 (q), 35.5 (q), 119.3 (d), 119.8 (d), 120.5 (s), 120.8 (s), 121.7 (s), 122.3 (d), 127.0 (d), 128.2 (s), 185.6 (s). Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.52; H, 4.85; N, 6.75. Found: C, 63.39; H, 5.06; N, 6.52.

3.3. General procedure for the preparation of 3-substituted isoindoles (9–33)

Method A: To a solution of 1-substituted-3-halo-isoindoles **5**–**8** (3 mmol) in anhydrous DMF (20 mL), TEA (0.42 mL, 3 mmol), and the proper nucleophile (6 mmol) were added. The reaction mixture was heated under reflux (0.5–2 h), and then after cooling, poured into ice-water. The resulting precipitate was collected by filtration, dried, and purified by chromatography column.

Method B: To a solution of 1-substituted-3-halo-isoindoles **7**,**8** (3 mmol) in anhydrous ethanol (30 mL), TEA (0.42 mL, 3 mmol), and the proper nucleophile (6 mmol) were added. The reaction mixture was heated at 50 °C (6–23 h). After cooling, the solvent was evaporated and the solid residue was stirred in water (25 mL). The resulting precipitate was filtered, dried and purified by chromatography column.

Method C: To a solution of 1-substituted-3-chloro-isoindoles **5**,**6** (3 mmol) in anhydrous DMF (20 mL), TEA (0.42 mL, 3 mmol), and the proper nucleophile (6 mmol) were added. The reaction mixture was heated by microwave irradiation using a Discovery Cem Reactor (150 W; 150 °C; 5 min), and then after cooling, poured into ice-water. The resulting precipitate was collected by filtration, dried, and purified by chromatography column.

Method D: A solution of 1-acetyl3-chloro-2-methyl-isoindole **8** (3 mmol) was heated under reflux for 24 h with an excess of pyrrolidine (30 mmol). The reaction mixture was heated at 50 °C (30 h). After cooling, the solvent was evaporated and the solid residue was stirred in water (25 mL). The resulting precipitate was filtered, dried and purified by chromatography column.

Method E: A solution of the proper nucleophile (6 mmol) in anhydrous acetonitrile (20 mL) was treated with finely powdered KOH (6 mmol) and dibenzo 18-crown-6 ether (0.09 g, 0.3 mmol) and stirred at room temperature for 30 min. The proper 1-substituted-3-halo-isoindoles **5**,**8** was added (10 mmol), and the reaction mixture was heated at 60 °C for 8–10 h 1 M hydrochloric acid was added and the solid was filtered off, dried, and purified by chromatography column.

3.3.1. 1-Carboxaldehyde-3-(phenylsulfanyl)-2H-isoindole (9). Chro matographic column (9:1 DCM/ethylacetate). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** cream crystals, yield 52% (Method A: reflux for 30 min), 81% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** cream crystals, yield 10% (Method A: reflux for 30 min), 66% (Method B: 50 °C for 20 h), 85% (Method C: 150 W; 150 °C; 5 min). Mp 145–147 °C. IR: 3379 (NH), 1632 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 7.15–7.34 (m, 6H, H-5, C_6H_5) 7.40 (t, J=7.9 Hz, 1H, H-6), 7.67 (d, J=7.9 Hz, 1H, H-4), 8.21 (d, J=7.9 Hz, 1H, H-7), 9.97 (s, 1H, CHO), 14.40 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 118.4 (s), 119.8 (d), 124.1 (d), 124.7 (s), 126.5 (d), 126.6 (d), 127.6 (d×2), 129.0 (s), 129.2 (d×3), 135.7 (s), 143.8 (s), 176.7 (d). Anal. Calcd for $C_{15}H_{11}NOS$: C, 71.12; H, 4.38; N, 5.53. Found: C, 71.42; H, 4.27; N, 5.19.

*3.3.2. 1-Carboxaldehyde-3-[(4-methoxyphenyl)sulfanyl]-2H-isoindole (**10**).* Chromatographic column (8:2 DCM/ethylacetate). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** cream needles, yield 73% (Method A: reflux for 30 min), 80% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** cream needles, yield 19% (Method A: reflux for 30 min), 57% (Method B: 50 °C for 16 h), 70% (Method C: 150 W; 150 °C; 5 min). Mp 154–156 °C. IR: 3436 (NH), 1610 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 3.72 (s, 3H, CH_3) 6.79 (d, J=8.7 Hz, 2H, H-3′, H-5′), 7.20 (t, J=7.4 Hz, 1H, H-5), 7.26 (t, J=7.4 Hz, 1H, H-6), 7.35 (d, J=8.7 z, H-2′, 2H, H-6′), 7.40 (d, J=7.4 Hz, 1H, H-4), 7.72 (d, J=7.4 Hz, 1H, H-7), 7.90–7.94 (br s, 1H, NH), 9.70 (s, 1H, CHO). ^{13}C NMR $CDCl_3$: δ 55.4 (q), 115.2 (s), 115.3 (d×2), 117.5 (s), 117.6 (d), 119.0 (s), 121.1 (d), 123.9 (d), 125.2 (s), 127.9 (d×2), 132.7 (s), 133.6 (d), 160.1 (s), 172.4 (d). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94. Found: C, 68.08; H, 4.79; N, 4.70.

*3.3.3. 1-Carboxaldehyde-3-[(4-methylphenyl)sulfanyl]-2H-isoindole (**11**).* Chromatographic column (9:1 DCM/ethylacetate). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** cream needles, yield 63% (Method A: reflux for 30 min), 65% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** cream needles, yield 25% (Method A: reflux for 30 min), 75% (Method B: 50 °C for 18 h), 82% (Method C: 150 W; 150 °C; 5 min). Mp 174–175 °C. IR: 3386 (NH), 1653 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.22 (s, 3H, CH_3), 7.12 (br s, 4H, C_6H_4), 7.23 (t, J=8.0 Hz, 1H, H-5), 7.38 (t, J=8.0 Hz, 1H, H-6), 7.65 (d, J=8.0 Hz, 1H, H-4), 8.18 (d, J=8.0 Hz, 1H, H-7), 9.93 (s, 1H, CHO) 14.41 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 20.4 (q), 119.7 (s), 119.8 (d), 123.9 (d), 124.3 (s), 124.4 (s), 126.5 (d), 128.4 (d×2), 128.9 (s), 129.9 (d), 130.0 (d×2), 131.7 (s), 136.5 (s), 176.5 (d). Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.60; H, 4.87; N, 5.52.

*3.3.4. 1-Carboxaldehyde-3-[(3-methoxyphenyl)sulfanyl]-2H-isoindole (**12**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** cream crystals, yield 60% (Method A: reflux for 45 min), 75% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** cream crystals, yield 13% (Method A: reflux for 30 min), 67% (Method B: 50 °C for 20 h), 78% (Method C: 150 W; 150 °C; 5 min). Mp 144–145 °C. IR: 3387 (NH), 1629 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 3.69 (s, 3H, CH_3), 6.65 (d, J=8.1 Hz, 1H, H-4′), 6.74 (s, 1H, H-2′), 6.79 (d, J=8.1 Hz, 1H, H-6′), 7.11 (t, J=8.1 Hz, 1H, H-5′), 7.29 (t, J=8.1 Hz, 1H, H-5), 7.40 (t, J=8.1 Hz 1H, H-6), 7.68 (d, J=8.1 Hz, 1H, H-4), 8.20

(d, *J*=8.1 Hz, 1H, H-7), 9.96 (br s, 1H, CHO), 14.30 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 55.1 (q), 112.0 (d), 113.1 (d), 119.5 (d), 119.7 (d), 124.1 (d), 124.7 (s×2), 126.5 (d), 129.2 (s), 130.3 (d×2), 137.0 (s×2), 159.7 (s), 176.7 (d). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94. Found: C, 67.54; H, 4.49; N, 5.10.

*3.3.5. 1-Acetyl-3-(phenylsulfanyl)-2H-isoindole (**13**).* Chromatograp hic column (98:2 DCM/ethylacetate). Cream crystals, yield 53% (Method A: reflux for 1 h), 30% (Method C: 150 W; 150 °C; 5 min). Mp 145–147 °C. IR: 3382 (NH), 1724 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.63 (s, 3H, CH_3), 7.10 (d, *J*=7.8 Hz, 2H, H-2′, H-6′) 7.20–7.34 (m, 4H, H-5, H-3′, H-5′, H4′), 7.34 (t, *J*=8.8 Hz, 1H, H-6), 7.64 (d, *J*=8.8 Hz, 1H, H-4), 8.19 (d, *J*=8.8 Hz, 1H, H-7), 13.93 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 27.6 (q), 114.9 (s), 119.6 (d), 121.2 (d), 123.4 (d), 124.2 (s), 126.0 (d), 126.1 (d), 126.2 (s), 126.9 (d×2), 129.3 (d×2), 129.4 (s), 136.5 (s), 185.8 (s). Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 72.11; H, 4.79; N, 4.98.

*3.3.6. 1-Acetyl-3-[(4-methoxyphenyl)sulfanyl]-2H-isoindole (**14**).* Chromatographic column (DCM). Cream crystals, yield 72% (Method A: reflux for 1 h), 31% (Method C: 150 W; 150 °C; 5 min). Mp 112–114 °C. IR: 3403 (NH), 1701 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.60 (s, 3H, CH_3), 3.69 (s, 3H, CH_3) 6.87 (d, *J*=8.8 Hz, 2H, H-3′, H-5′) 7.17 (t, *J*=7.9 Hz, 1H, H-5), 7.27 (d, *J*=8.8 Hz, 2H, H-2′, H-6′), 7.31 (t, *J*=7.9 Hz, 1H, H-6), 7.69 (d, *J*=7.9 Hz, 1H, H-4), 8.14 (d, *J*=7.9 Hz, 1H, H-7) 13.82 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 27.6 (q), 55.0 (q), 115.0 (d×2), 117.6 (s), 119.8 (d), 121.0 (d), 123.1 (d), 123.6 (s), 125.9 (s), 126.0 (d), 127.0 (s), 128.8 (s), 130.9 (d×2), 158.6 (s), 185.8 (s). Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.93; H, 5.21; N, 4.39.

*3.3.7. 1-Acetyl-3-[(4-methylphenyl)sulfanyl]-2H-isoindole (**15**).* Chromatographic column (DCM). Cream crystals, yield 72% (Method A: reflux for 1 h), 37% (Method C: 150 W; 150 °C; 5 min). Mp 129–131 °C. IR: 3382 (NH), 1655 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.21 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.07–7.12 (m, 4H, C_6H_4), 7.18 (t, *J*=8.5 Hz, 1H, H-5), 7.34 (t, *J*=8.5 Hz, 1H, H-6), 7.65 (d, *J*=8.5 Hz, 1H, H-4), 8.19 (d, *J*=8.5 Hz, 1H, H-7), 13.89 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 20.4 (q), 27.6 (q), 117.0 (s), 119.7 (d), 121.1 (d), 123.3 (d), 124.0 (s), 126.0 (d), 127.1 (s), 127.8 (d×2), 129.2 (s), 129.9 (d×2), 132.7 (s), 136.0 (s), 185.7 (s). Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.41; H, 5.61; N, 5.23.

*3.3.8. 1-Acetyl-3-[(3-methoxyphenyl)sulfanyl]-2H-isoindole (**16**).* Chromatographic column (DCM). Cream crystals, yield 80% (Method A: reflux for 1.5 h), 36% (Method C: 150 W; 150 °C; 5 min). Mp 102–105 °C. IR: 3380 (NH), 1645 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.63 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 6.63 (d, *J*=8.3 Hz, 1H, H-4′), 6.70 (s, 1H, H-2′), 6.75 (d, *J*=8.3 Hz, 1H, H-6′), 7.15–7.24 (m, 2H, H-5′, H-5), 7.35 (t, *J*=8.3 Hz, 1H, H-6), 7.66 (d, *J*=8.3 Hz, 1H, H-4), 8.20 (d, *J*=8.3 Hz, 1H, H-7), 13.93 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 27.6 (q), 55.1 (q), 111.6 (d), 112.8 (d), 114.8 (s), 119.1 (d), 119.6 (d), 121.2 (d), 123.5 (d), 124.3 (s), 126.0 (d), 127.0 (s), 129.5 (s), 130.2 (d), 137.9 (s), 159.7 (s), 185.9 (s). Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.93; H, 5.18; N, 4.37.

*3.3.9. 1-Acetyl-2-methyl-3-(phenylsulfanyl)-2H-isoindole (**17**).* Chromatographic column (DCM). Cream solid, yield 99% (Method B: 50 °C for 18 h). Mp 95–96 °C. IR: 1626 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 2.74 (s, 3H, CH_3), 4.26 (s, 3H, CH_3), 6.92 (d, *J*=6.8 Hz, 2H, H-2′, H-6′), 7.08–7.20 (m, 4H, H-5, H-3′, H-4′, H-5′), 7.32 (t, *J*=8.7 Hz, 1H, H-6), 7.80 (d, *J*=8.7 Hz, 1H, H-4), 7.89 (d, *J*=8.7 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 31.0 (q), 36.0 (q), 120.0 (d), 120.7 (d), 121.8 (s), 123.1 (d), 124.6 (s), 126.2 (d), 126.3 (d), 126.7 (d×2), 128.1 (s), 129.3 (d×2), 129.8 (s), 135.9 (s), 187.0 (s). Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.80; H, 5.27; N, 4.66.

*3.3.10. 1-Acetyl-3-[(4-methoxyphenyl)sulfanyl]-2-methyl-2H-isoindole (**18**).* Chromatographic column (DCM). Cream needles, yield 70% (Method B: 50 °C for 20 h). Mp 85–86 °C. IR: 1626 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 2.76 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.31 (s, 3H, CH_3), 6.74 (d, 2H, *J*=8.7 Hz, H-3′, H-5′), 7.04 (d, *J*=8.7 Hz, 2H, H-2′, H-6′), 7.20 (t, *J*=7.7 Hz, 1H, H-5), 7.35 (t, *J*=7.7 Hz, 1H, H-6), 7.87 (d, *J*=7.7 Hz, 1H, H-4), 7.91 (d, *J*=7.7 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 30.9 (q), 36.2 (q), 55.4 (q), 115.1 (d), 118.2 (s), 120.0 (d×2), 120.9 (d), 123.0 (d), 125.8 (s), 126.4 (d×2), 128.3 (s), 129.5 (s), 130.1 (d), 148.5 (s), 159.8 (s), 194.2 (s). Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.18; H, 5.55; N, 4.63.

*3.3.11. 1-Acetyl-2-methyl-3-[(4-methylphenyl)sulfanyl]-2H-isoindole (**19**).* Chromatographic column (DCM). Cream crystals, yield 98% (Method B: 50 °C for 18 h). Mp 107–108 °C. IR: 1624 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 2.26 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.30 (s, 3H, CH_3), 6.88–7.03 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.20 (t, *J*=8.4 Hz, 1H, H-5), 7.36 (t, *J*=8.4 Hz, 1H, H-6), 7.85 (d, *J*=8.4 Hz, 1H, H-4), 7.93 (d, *J*=8.4 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 20.9 (q), 31.0 (q), 36.1 (q), 120.0 (d), 120.8 (d), 123.0 (d), 123.2 (s), 124.6 (s), 126.4 (d), 127.4 (d×2), 128.2 (s), 130.1 (d×2), 133.9 (s), 136.5 (s), 138.8 (s), 187.0 (s). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.34; H, 5.77; N, 4.56.

*3.3.12. 1-Acetyl-3-[(3-methoxyphenyl)sulfanyl]-2-methyl-2H-isoindole (**20**).* Chromatographic column (DCM). Cream solid, yield 80% (Method B: 50 °C for 20 h). Mp 84–85 °C. IR: 1626 (CO) cm^{-1}. ^{1}H NMR $CDCl_3$: δ 2.75 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 4.27 (s, 3H, CH_3), 6.46–6.50 (m, 2H, H-2′, H-4′), 6.64 (d, *J*=7.8 Hz, 1H, H-6′), 7.07 (t, *J*=8.0 Hz, 1H, H-5), 7.17 (t, *J*=8.0 Hz, 1H, H-6), 7.33 (t, *J*=7.8 Hz, 1H, H-5′), 7.80 (d, *J*=8.0 Hz, 1H, H-4), 7.90 (d, *J*=8.0 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 31.0 (q), 36.0 (q), 55.2 (q), 111.5 (d), 112.6 (d), 118.9 (d), 120.0 (d), 120.6 (d), 121.5 (s), 123.1 (d), 124.7 (s), 126.3 (d), 128.1 (s), 128.9 (s), 130.1 (d), 137.2 (s), 160.1 (s), 187.0 (s). Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.71; H, 5.45; N, 4.22.

*3.3.13. 1-Carboxaldehyde-3-[(4-methoxybenzyl)amino]-2H-isoindole (**21**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown solid, yield 60% (Method A: reflux for 1 h), 89% (Method B: 50 °C for 9 h), 66% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown solid, 100% (Method B: 50 °C for 9 h). Mp 140–141 °C. IR: 3376 (NH), 3190 (NH), 1650 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 3.73 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 6.93 (d, *J*=8.4 Hz, 2H, H-3′, H-5′), 7.13 (t, *J*=6.9 Hz, 1H, H-5), 7.26 (t, *J*=6.9 Hz, 1H, H-6), 7.31 (d, *J*=8.4 Hz, 2H, H-2′, H-6′), 7.49 (d, *J*=6.9 Hz, 1H, H-4), 7.78 (d, *J*=6.9 Hz, 1H, H-7), 8.00 (s, 1H, NH), 8.07 (s, 1H, CHO), 9.16 (s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 51.7 (t), 55.0 (q), 113.8 (d×2), 116.7 (d), 118.7 (d), 121.8 (s), 122.6 (d), 125.9 (d), 128.8 (d×2), 129.2 (s), 129.5 (s), 130.9 (s), 138.7 (s), 142.6 (d), 157.1 (s). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.51; H, 5.88; N, 10.06.

3.3.14. 1-Carboxaldehyde-3-[(4-methylbenzyl)amino]-2H-isoindole (22). Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown solid, yield 60% (Method A: reflux for 1.5 h), 64% (Method B: 50 °C for 10 h), 55% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown solid, 98% (Method B: 50 °C for 10 h). Mp 67–69 °C. IR: 3376 (NH), 3189 (NH), 1650 (CO) cm^{-1}. ^{1}H NMR DMSO-d_6: δ 2.28 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.11–7.30 (m, 6H, H-5, H-6, H-2′, H-3′, H-5′, H-6′), 7.42 (d, *J*=7.4 Hz, 1H, H-4), 7.78 (d, *J*=7.4 Hz, 1H, H-7), 8.03 (s, 1H, NH), 8.10 (s, 1H, CHO), 9.33 (br s, 1H, NH). ^{13}C NMR DMSO-d_6:

δ 20.7 (q), 51.3 (t), 116.7 (d), 119.4 (d), 122.3 (d), 123.9 (s), 126.0 (d), 127.4 (d×2), 127.9 (s), 129.1 (d×2), 131.9 (s), 135.9 (s), 136.5 (s), 138.5 (s), 143.0 (d). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.49; H, 6.13; N, 10.31.

*3.3.15. 3-(Benzylamino)-1-carboxaldehyde-2H-isoindole (**23**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown solid, yield 53% (Method A: reflux for 1.5 h), 50% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown solid, 96% (Method B: 50 °C for 18 h). Mp 111–112 °C. IR: 3377 (NH), 3195 (NH), 1650 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 4.57 (d, *J*=4.8 Hz, 2H, CH_2), 7.14 (t, *J*=7.3 Hz, 1H, H-5), 7.24–7.39 (m, 6H, C_6H_5, H-6), 7.50 (d, *J*=7.3 Hz, 1H, H-4), 7.79 (d, *J*=7.3 Hz, 1H, H-7), 8.03 (s, 1H, NH), 8.10 (s, 1H, CHO), 9.35 (t, *J*=4.8 Hz, 1H, NH). ^{13}C NMR DMSO-d_6: δ 51.4 (t), 116.8 (d), 118.7 (d), 121.9 (s), 122.3 (d), 126.0 (d), 127.2 (d), 127.4 (d×2), 128.5 (d×2), 129.6 (s), 138.7 (s), 139.0 (s), 139.6 (s), 142.8 (d). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.92; H, 5.69; N, 10.97.

*3.3.16. 3-[Benzyl(methyl)amino]-1-carboxaldehyde-2H-isoindole (**24**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown solid, yield 50% (Method A: reflux for 1.5 h), 51% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown solid, 80% (Method B: 50 °C for 23 h). Mp 105–106 °C. IR: 3376 (NH), 1633 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 3.62 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 7.20 (t, *J*=7.6 Hz, 1H, H-5), 7.34 (t, *J*=7.6 Hz, 1H, H-6), 7.35–7.40 (m, 5H, C_6H_5), 7.54 (d, *J*=7.6 Hz, 1H, H-4), 7.96 (d, *J*=7.6 Hz, 1H, H-7), 8.03 (br s, 1H, NH), 8.24 (s, 1H, CHO). ^{13}C NMR DMSO-d_6: δ 38.2 (q), 61.2 (t), 117.1 (d), 118.5 (d), 122.7 (d), 123.5 (s), 125.8 (d), 127.7 (d×2), 127.8 (d), 128.8 (d×2), 130.3 (s), 131.1 (s), 136.3 (s), 140.6 (s), 141.1 (d). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.53; H, 6.22; N, 10.34.

*3.3.17. 1-Carboxaldehyde-3-pyrrolidin-1-yl-2H-isoindole (**25**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown needles, yield 70% (Method A: reflux for 2 h), 71% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown needles, 99% (Method B: 50 °C for 6 h). Mp 108–109 °C. IR 3391 (NH), 1631 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 1.90 (q, *J*=6.4 Hz, 2H, CH_2), 2.01 (q, *J*=6.4 Hz, 2H, CH_2), 3.78 (t, *J*=6.4 Hz, 2H, CH_2), 3.92 (t, *J*=6.4 Hz, 2H, CH_2), 7.16 (t, *J*=7.6 Hz, 1H, H-5), 7.29 (t, *J*=7.6 Hz, 1H, H-6), 7.51 (d, *J*=7.6 Hz, 1H, H-4), 7.87 (d, *J*=7.6 Hz, 1H, H-7), 8.14 (s, 1H, CHO), 14.40 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 24.2 (t), 25.5 (t), 50.8 (t), 53.9 (t), 116.8 (d), 118.9 (d), 122.3 (d), 123.9 (s), 125.2 (d), 129.4 (s), 131.0 (s), 138.1 (d), 139.5 (s). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.58; H, 6.63; N, 13.27.

*3.3.18. 3-(Benzylamino)-1-acetyl-2H-isoindole (**26**).* Chromatographic column (98:2 DCM/ethylacetate). Brown solid, yield 9% (Method B: 50 °C for 19 h). Mp 101–103 °C. IR: 3357 (NH), 3193 (NH), 1597 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 2.53 (s, 3H, CH_3), 4.66 (d, *J*=6.6 Hz, 2H, CH_2), 7.13 (t, *J*=7.6 Hz, 1H, H-5), 7.25–7.38 (m, 6H, H-6, C_6H_5), 7.54 (d, *J*=7.6 Hz, 1H, H-4), 7.77 (d, *J*=7.6 Hz, 1H, H-7), 8.30 (br s, 1H, NH), 9.24 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 14.8 (q), 45.7 (t), 119.2 (d), 119.3 (d), 121.4 (d), 123.2 (s), 126.1 (d), 126.9 (d×2), 127.1 (d), 128.6 (d×2), 134.5 (s), 135.8 (s), 136.7 (s), 139.0 (s), 156.0 (s). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.40; H, 6.14; N, 10.46.

*3.3.19. 1-Acetyl-3-pyrrolidin-1-yl-2H-isoindole (**27**).* Chromatographic column (DCM). Cream needles, yield 33% (Method B: 50 °C for 18 h). Mp 168–169 °C. IR 3391 (NH), 1645 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 1.79–2.01 (m, 4H, $CH_{2\times}2$), 2.73 (s, 3H, CH_3), 3.79 (br s, 2H, CH_2), 4.10 (br s, 2H, CH_2), 7.14 (t, *J*=8.2 Hz, 1H, H-5), 7.28 (t, *J*=8.2 Hz, 1H, H-6), 7.56 (d, *J*=8.2 Hz, 1H, H-4), 7.85 (d, *J*=8.2 Hz, 1H, H-7) 14.4 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 19.9 (q), 23.8 (t), 25.6 (t), 51.1 (t), 54.5 (t), 89.5 (s), 107.5 (s), 118.6 (d), 120.2 (s), 120.3 (d), 121.4 (d), 125.1 (d), 129.2 (s), 153.5 (s). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.44; H, 7.16; N, 12.50.

*3.3.20. 1-Acetyl-1-methyl-3-pyrrolidin-1-yl-2H-isoindole (**28**).* Chromatographic column (95:5 DCM/ethylacetate). Cream solid, yield 41% (Method D: reflux for 30 h). Mp 75–78 °C. IR: 1685 (CO) cm^{-1}. ^1H NMR $CDCl_3$: δ 1.26 (s, 3H, CH_3) 1.74–1.81 (m, 4H, CH_2), 2.54–2.66 (m, 2H, CH_2), 2.72–2.89 (m, 2H, CH_2), 3.13 (s, 3H, CH_3), 7.45 (t, *J*=6.5 Hz, 1H, H-5), 7.47–7.55 (m, 2H, H-6, H-4), 7.81 (d, *J*=6.5 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 24.3 (t×2), 29.7 (q), 46.8 (t×2), 76.5 (q), 123.2 (d), 123.3 (d), 128.8 (d), 130.9 (s), 131.2 (d), 132.9 (s), 133.9 (s), 143.1 (s), 167.7 (s). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.54; H, 7.52; N, 11.35.

*3.3.21. 1-Carboxaldehyde-3-(4-methoxyphenoxy)-2H-isoindole (**29**).* Chromatographic column (98:2 DCM/ethylacetate). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** white solid, yield 8% (Method A: reflux for 10 h), 35% (Method C: 150 W; 150 °C; 5 min); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** white solid, 15% (Method B: 50 °C for 16 h). Mp 133–135 °C. IR: 3415 (NH), 1644 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 3.33 (s, 3H, CH_3), 7.56 (t, *J*=7.8 Hz, 1H, H-5), 7.64 (t, *J*=7.8 Hz, 1H, H-6), 7.74 (d, *J*=7.8 Hz, 2H, H-3′, H-5′), 7.86 (d, *J*=7.8 Hz, 2H, H-2′, H-6′), 7.90 (br s, 1H, CHO), 8.63 (d, *J*=7.8 Hz, 1H, H-4), 8.93 (d, *J*=7.8 Hz, 1H, H-7), 11.31 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 40.6 (q), 120.3 (s), 120.7 (d), 123.3 (d), 123.4 (d), 124.2 (s), 127.9 (d×2), 128.3 (d), 129.4 (s), 129.7 (d×2), 130.1 (s), 131.3 (d), 133.2 (d), 136.4 (s), 136.7 (s), 169.6 (d). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.69; H, 4.83; N, 5.48.

*3.3.22. 2-(1-Carboxaldehyde-2H-isoindole-3-yl)-malono-nitrile (**30**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** brown solid, yield 40% (Method B: 50 °C for 12 h), 70% (Method C: 150 W; 150 °C; 5 min), 15% (Method E: reflux for 8 h); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** brown solid, 51% (Method B: 50 °C for 8 h), 40% (Method C: 150 W; 150 °C; 5 min). Mp 155–158 °C. IR: 3221 (NH), 2204 (CN), 2208 (CN), 1628 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 4.45 (s, 1H, CH), 7.34 (t, *J*=7.8 Hz, 1H, H-5), 7.50 (t, *J*=7.8 Hz, 1H, H-6), 7.70 (d, *J*=7.8 Hz, 1H, H-4), 8.02 (br s, 1H, CHO), 8.17 (d, *J*=7.8 Hz, 1H, H-7), 10.25 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 60.0 (d), 117.0 (s), 117.8 (s), 118.7 (s), 119.8 (d×2), 120.3 (s), 124.5 (s), 124.8 (d), 126.3 (s), 128.5 (d), 140.1 (d). Anal. Calcd for $C_{12}H_7N_3O$: C, 68.89; H, 3.37; N, 20.09. Found: C, 68.66; H, 3.40; N, 20.28.

*3.3.23. Ethyl 2-cyano-2-(1-carboxaldehyde-2H-isoindole-3-yl)-acetate (**31**).* Chromatographic column (DCM). From 1-carboxaldehyde-3-chloro-2*H*-isoindole **5** cream solid, yield 40% (Method B: 50 °C for 20 h), 20% (Method C: 150 W; 150 °C; 5 min), 15% (Method E: reflux for 10 h); from 3-bromo-1-carboxaldehyde-2*H*-isoindole **7** cream solid, 40% (Method B: 50 °C for 20 h), 30% (Method C: 150 W; 150 °C; 5 min). Mp 127–128 °C. IR: 3373 (NH), 2204 (CN), 1674 (CO), 1618 (CO) cm^{-1}. ^1H NMR DMSO-d_6: δ 1.29 (t, *J*=7.4 Hz, 3H, CH_3), 2.50 (s, 1H, CH), 4.25 (q, *J*=7.4 Hz, 2H, CH_2), 7.33 (t, *J*=8.1 Hz, 1H, H-5), 7.47 (t, *J*=8.1 Hz, 1H, H-6), 7.70 (d, *J*=8.1 Hz, 1H, H-4), 8.17 (s, 1H, CHO), 8.31 (d, *J*=8.1 Hz, 1H, H-7), 10.75 (br s, 1H, NH). ^{13}C NMR DMSO-d_6: δ 13.8 (q), 61.9 (t), 85.2 (s), 115.0 (s), 117.1 (s), 119.7 (d×2), 121.1 (s), 121.4 (d), 124.3 (s), 124.5 (d), 127.7 (d), 138.3 (d), 164.3 (s). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.81; H, 4.75; N, 10.73.

*3.3.24. 2-(1-Acetyl-1-methyl-2H-isoindole-3-yl)-malono-nitrile (**32**).* Chromatographic column (DCM). Brown solid, yield 30% (Method B: 50 °C for 20 h), 28% (Method C: 150 W; 150 °C; 5 min), 16% (Method E: reflux for 10 h). Mp 103–104 °C. IR: 2193 (CN), 1624

(CO) cm^{-1}. ^1H NMR $CDCl_3$: δ 1.96 (s, 3H, CH_3) 3.17 (s, 3H, CH_3), 4.92 (s, 1H, CH), 7.45 (d, J=6.6 Hz, 1H, H-4), 7.50–7.58 (m, 2H, H-6, H-5), 7.87 (d, J=6.6 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 24.1 (q), 28.9 (q), 72.1 (d), 122.5 (d), 123.2 (s), 124.1 (d), 129.5 (d), 132.0 (s), 132.2 (d), 134.0 (s), 138.5 (s×2), 169.1 (s), 204.4 (s). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.67; H, 4.74; N, 17.85.

*3.3.25. 1-Acetyl-3-cyano-2-methyl-2H-isoindole (**33**).* Chromatographic column (DCM). White solid, yield 70% (Method A: reflux for 5 h), 10% (Method B: 50 °C for 20 h). Mp 118–119 °C. IR: 2212 (CN), 1649 (CO) cm^{-1}. ^1H NMR $CDCl_3$: δ 2.79 (s, 3H, CH_3) 4.34 (s, 3H, CH_3), 7.32 (t, J=8.1 Hz, 1H, H-5), 7.40 (t, J=8.1 Hz, 1H, H-6), 7.75 (d, J=8.1 Hz, 1H, H-4), 7.95 (d, J=8.1 Hz, 1H, H-7). ^{13}C NMR $CDCl_3$: δ 31.1 (q), 38.1 (q), 104.6 (s), 112.4 (s), 118.9 (d), 120.4 (d), 125.3 (d), 125.5 (s), 126.6 (d), 129.4 (s), 133.8 (s), 188.1 (s). Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.86; H, 5.15; N, 13.98.

3.4. Docking

The reported 3D structure of two tubulin dimers cocrystalized with stathmin-like domain and *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine (DAMA–colchicine), was downloaded from the PDB data bank (http://www.rcsb.org/pdb; PDB code: 1SA0).[18] All docking runs were performed into the colchicine binding site of the tubulin, using GLIDE 15 software,[19] with its XP mode default parameters. GLIDE output consists of a score named GSCORE, where a more negative value indicates a higher binding affinity. To validate the use of GLIDE program, the docking studies were performed on the reference compounds colchicine and combrestatin A-4. GLIDE successfully reproduced the binding conformations reported in literature with acceptable root-mean-square deviation (RMSD) of atom coordinates.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.056.

References and notes

1. Bonnett, R.; North, S. A. In *Advances in Heterocycles Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; 1981; Vol. 29, pp 341–399.
2. Babichev, F. S.; Kovtunenko, V. A.; Tyltin, A. K. *Russ. Chem. Rev.* **1981**, *50*, 1087–1103.
3. Hordiyenko, O. V.; Rudenko, I. V.; Biitseva, A. V.; Turov, A. V.; Arrault, A.; Brosse, N.; Fabre, O.; Jamart-Grègoire, B.; Zubatyuk, R. I.; Shishkin, O. V. *Tetrahedron* **2009**, *65*, 6218–6225.
4. Cirrincione, G.; Almerico, A. M.; Passannanti, A.; Diana, P.; Mingoia, F. *Synthesis* **1997**, 1169–1173.
5. Barraja, P.; Diana, P.; Carbone, A.; Cirrincione, G. *Tetrahedron* **2008**, *64*, 11625–11631.
6. Barraja, P.; Spanò, V.; Diana, P.; Carbone, A.; Cirrincione, G.; Vedaldi, D.; Salvador, A.; Viola, G.; Dall'Acqua, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1711–1714.
7. Barraja, P.; Spanò, V.; Diana, P.; Carbone, A.; Cirrincione, G. *Tetrahedron Lett.* **2009**, *50*, 5389–5391.
8. Allison, B.; Rabinowitz, M.H. Patent WO 2008124518, 2008; *Chem. Abstr.* **2008**, *149*, 448404.
9. Cirrincione, G.; Diana, P. WO 2008041264, 2008; *Chem. Abstr.* **2008**, *148*, 426916.
10. Cheng, Y.; Tomaszewski, M.; Yang, H. WO 2007139464, 2007; *Chem. Abstr.* **2007**, *148*, 54892.
11. Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Dall'Acqua, F.; Salvador, A.; Vedaldi, D.; Basso, G.; Viola, G. *J. Med. Chem.* **2008**, *51*, 2387–2399.
12. La Regina, G.; Edler, M. C.; Brancale, A.; Kandil, S.; Colluccia, A.; Piscitelli, F.; Hamel, E.; De Martino, G.; Matesanz, R.; Diaz, J. F.; Scovassi, A. I.; Prosperi, E.; Lavecchia, A.; Novellino, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2007**, *50*, 2865–2874.
13. von Dobeneck, H.; Reinhard, H.; Dueubel, H.; Wolkenstein, D. *Chem. Ber.* **1969**, *102*, 1357–1362.
14. Nagle, A.; Hur, W.; Gray, N. S. *Curr. Drug Targets* **2006**, *7*, 305–326.
15. Pasquier, E.; Andrè, N.; Braguer, D. *Curr. Cancer Drug Targets* **2007**, *7*, 566–581.
16. Pettit, G. R.; Singh, S. G.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. *J. Med. Chem.* **1995**, *38*, 1666–1672.
17. Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253–265.
18. Ravelli, R. B.; Gigant, B.; Curmi, P. A.; Jourdan, I.; Lachkar, S.; Sobel, A.; Knossow, M. *Nature* **2004**, *428*, 198–202.
19. *15 GLIDE Version 4.5, Prime, Version 1.6*; Schrödinger LLC: New York, NY, 2007.