European Journal of Medicinal Chemistry 60 (2013) 365–375

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Diminutive effect on T and B-cell proliferation of non-cytotoxic α-santonin derived 1,2,3-triazoles: A report

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ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form
16 November 2012
Accepted 8 December 2012
Available online 17 December 2012

Keywords:
α-Santonin
α-Desmotroposantonin-1,2,3-triazoles
Immunosuppressant
ConA
LPS

ABSTRACT

α-Santonin derived new series of 1,2,3-triazoles synthesized through Azide–Alkyne Huisgen 1,3-dipolar cycloaddition reaction between substituted aryl azide and a propargylated α-desmotrosantonin were bio-evaluated for their diminutive effect on ConA induced T-cell and LPS induced B-cell proliferation. Interestingly, most of the synthesized compounds showed better immunosuppressant activity than α-santonin. Triazole derivatives **9**, **10**, **17**, **18**, **29**, and **30** displayed significant diminutive effect on cell proliferation. Compounds **12** and **13** were found selective against ConA T-cell proliferation exhibiting >90% inhibition at 1×10^{-6} M concentration. The present study resulted in identification of several triazole derivatives as effective immunosuppressive agents.

1. Introduction

Natural products (NPs) from plant, microbial and mammalian source have been a reliable and constant source of therapeutic agents for the use in humans, besides affording rich source of nutraceuticals and food supplement and the quest to swell these numbers goes unabated [1]. While the discovery of natural products penicillin and lovastatin led to development of new drug armamentariums, tailoring of many natural product scaffolds by the chemists has proved equally rewarding in the development of some of the most effective drugs such as antidiabetic drug metformin (from galgine), hypertensive drug verapamil (from papaverine), and anti-asthmatic drug sodium cromoglycate (from khellin). The role of NPs and/or natural product scaffolds shall continue to play a highly significant role in the drug discovery and development process for the treatment of human diseases [2–4].

Immunosuppressant is an imperative class of clinical drugs for an array of medical processes, including transplant rejection and the treatment of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, and psoriasis [5–7]. The FDA approval of cyclosporine (CsA) in 1983 was a milestone in organ transplantation. T-lymphocytes play an integral role in transplant rejection and autoimmune diseases [8]. Several natural products from plants and microorganisms (Fig. 1) are reported with clinically important therapeutic immunosuppressant activity [7,9–12]. Although immunosuppressive drugs have been used in clinic for organ transplantation and treatment of autoimmune diseases, their side effects including liver toxicity, renal toxicity, infection, malignancy, and others cannot be neglected [13–18]. Thus, there is a pressing need for novel potential immunosuppressive agents with high efficacy and low toxicity.

α-Santonin (**1**), from *Artemisia* species has been used extensively in traditional Indian and Chinese medicine for the treatment of inflammation and other conditions [19]. This NP and its derivatives prepared through different synthetic routes have been found active against various human cancer cell lines and many of them showing more potency than the parent molecule [20–22] besides having antipyretic activity [23]. Its derivatives such as cyclic peroxide and BIOS-based libraries are reported to possess antimalarial activity (ED_{50} = 728.59 ng/mL) [24] and 5-lipoxygenase inhibitory activity (IC_{50} = 0.8 μM) [25,26] (Fig. 2).

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http://dx.doi.org/10.1016/j.ejmech.2012.12.018

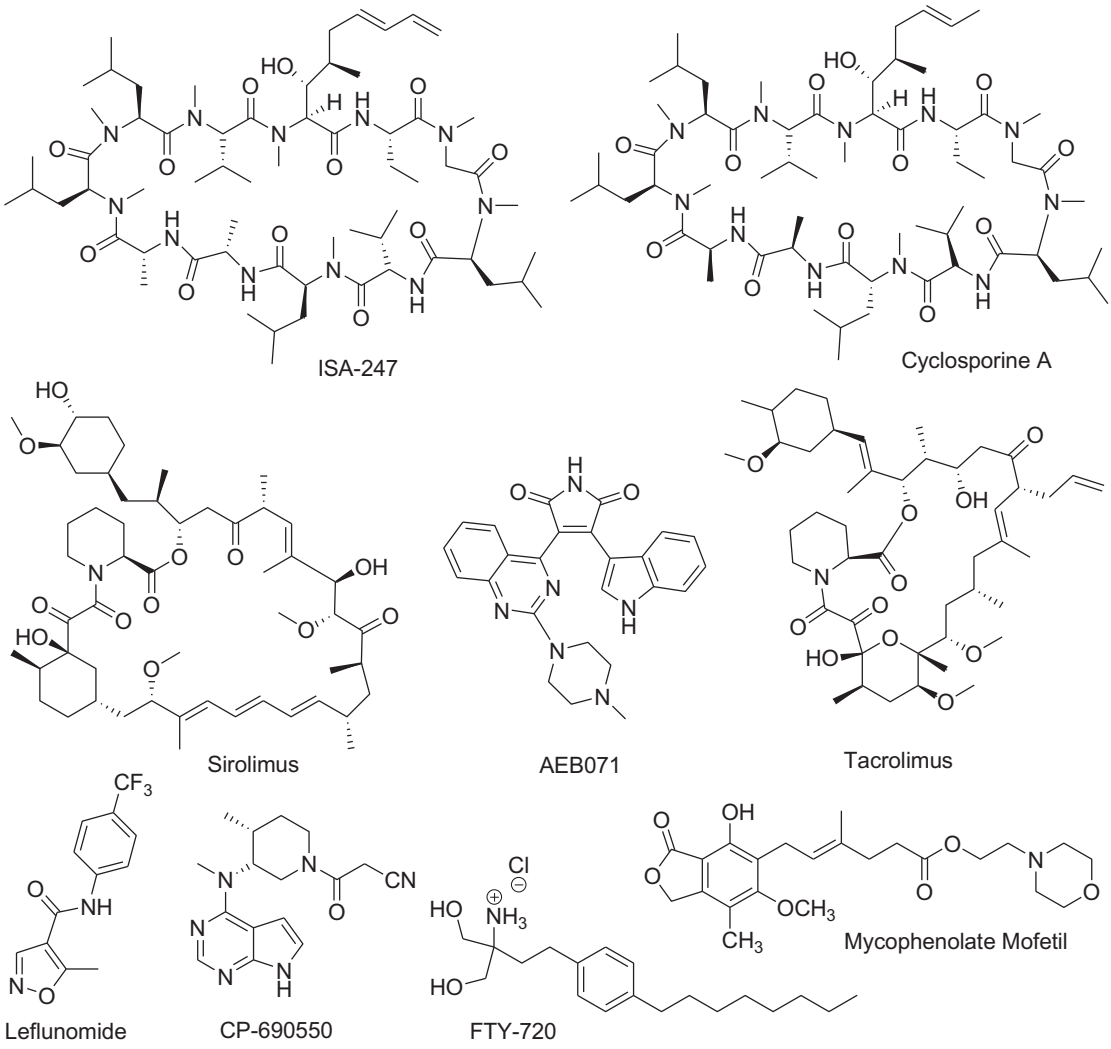


Fig. 1. Some of the selected potent immunosuppressant agents.

In the present study, the unexplored immunosuppressant property of α-santonin derived α-desmotroposantonin 1,2,3-triazole analogues carrying diverse chemical features at N-1 position have been investigated. Huisgen 1,3-dipolar cycloaddition reaction has gained interest due to interesting biological activity of 1,2,3-triazoles [27–31].

2. Result and discussion

2.1. Chemistry

In the present study, α-santonin **1** isolated from the aerial part of *Artemisia laciniata* was used as the starting material. The NP was subjected to rearrangement [32] with Ac_2O/H_2SO_4 to get acetyl α-desmotroposantonin (**2**) which on deacetylation afforded α-desmotroposantonin (**3**). Propargylated α-desmotroposantonin (**4**) obtained by propargylation [33] of **3** was subjected to Copper(I)-catalyzed one pot cycloaddition reaction (click chemistry strategy) with various substituted aromatic azides generated in situ by aryl boronic acids in methanol and water (1:1) in the presence of sodium ascorbate (reducing agent) [34] to give 1,2,3-triazol-1-yl desmotroposantonin derivatives (**5**–**31**) in excellent yields (Scheme 1). All the synthesized compounds (**2**–**31**) were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectroscopic analysis.

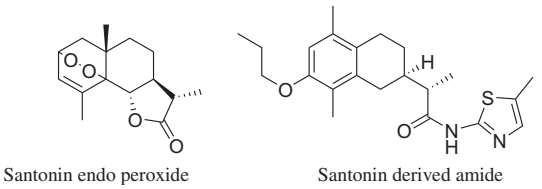
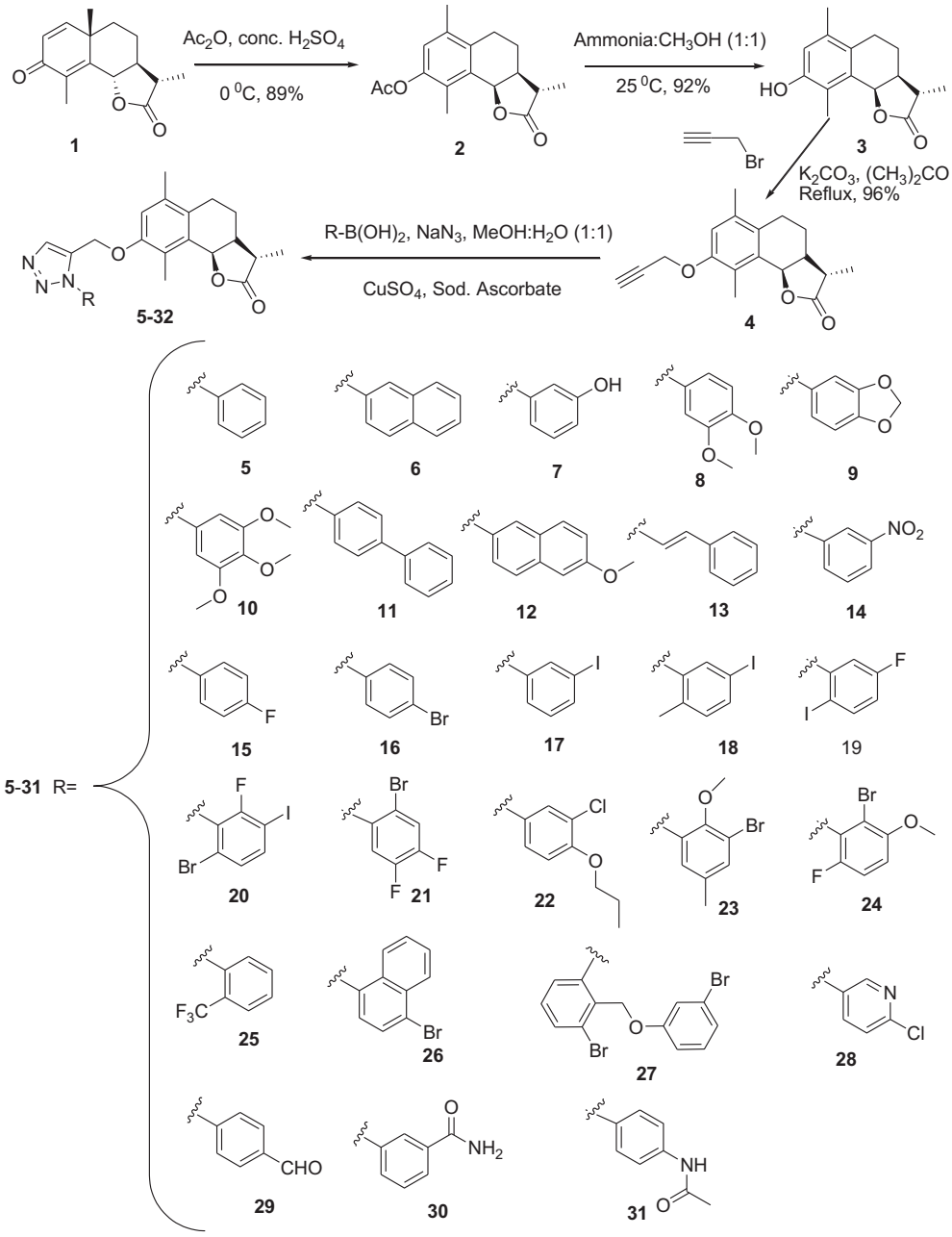


Fig. 2. Bioactive analogues of santonin.

2.2. Biology

α-Santonin (**1**), its A-ring rearranged derivative (A-ring aromatized) bearing C-3-acetyl group (**2**), the deacetylated product (**3**), and compound **4** (the propargylated derivative of **3**) were tested for cell proliferation against ConA induced T-cell and LPS induced B-cells (Table 1). In comparison to the parent compound **1**, compound **2** displayed enhanced bioactivity against LPS induced B-cell proliferation in a dose dependent manner. It showed least cytotoxicity which was also observed in the parent molecule. The compound however, showed no inhibition against ConA induced T-cell proliferation. No diminutive effect against the two mitogens was observed for compound **3**, but in case of compound **4** (which showed cytotoxicity) only LPS induced B-cell



Scheme 1. Synthesis of substituted aryl 1,2,3-triazole α-desmotroposantonin chemical entities.

proliferation was observed. The 1,2,3-triazoles anchored through OH functionality at C-3 position of **1** were evaluated against the two mitogens. Among triazoles, compounds **5**, **6** and **11** bearing unsubstituted aryl moiety at N-1 position were found having insignificant activity besides being cytotoxic. For compounds **7**, **12**–**18**, **25**, **26**, and **28**–**31** with halo, nitro, alkyloxy, halo alkyl and hydroxyl group/s in the aryl part of the molecule (encompassing both electron donating and withdrawing groups) showed variable proliferation effect against the two mitogens. Compound **7** displayed marginal LPS induced B-cell proliferation effect. While compounds **12** and **13** showed high degree of selectivity for T-cell lymphocytes to exhibit high diminutive effect (>90% inhibition) at all the three doses, LPS induced B-cell proliferation (>90% at 10^{-5} M conc.) was observed only for compound **12**. Both the compounds were non-cytotoxic, which is an important attribute for an immunosuppressive agent of clinical application such as cyclosporine A [35,36]. ConA induced T-cell proliferation effect similar to **13** was also observed for cytotoxic compound **14** but failed to show any effect against the other mitogen. Non-cytotoxic compound **17** and **18** showed inhibition (maximum effect 20% at 10^{-5} M conc. for **17** and 26% at 10^{-5} M conc. and ~35% at 10^{-6} M conc. for **18**) against ConA and LPS mitogens. For non-cytotoxic compounds **29** and **30**, inhibition at all the three dose levels was observed against ConA and LPS induced cell proliferation, with latter showing higher inhibitory effect. The rest of the compounds did not show any significant activity against the mitogens. Among **8**–**10**, **19**–**24** and **27**, a group of di- and tri-substituted aryl triazole derivatives, non-cytotoxic compounds **9** and **10** displayed inhibitory effect against LPS and ConA induced cell proliferation. Surprisingly, compound **8** did not show any diminutive effect and

Table 1
Effect at three different concentrations (1×10^{-4}, 1×10^{-5} and 1×10^{-6} M) of compounds **1**–**31** on ConA and LPS induced murine lymphocyte proliferation (10 μg/mL).

Entry	Conc.(M)	Cytotoxicity	ConA Mean + SE	ConA-induced T cell proliferation rate (%)	LPS mean + SE	LPS-induced B cell proliferation rate (%)
1	10^{-4}	−	0.77 ± 0.05	−6.09	0.74 ± 0.01	−36.75
	10^{-5}	−	0.85 ± 0.10	+3.65	0.78 ± 0.03	−25.64
	10^{-6}	−	0.49 ± 0.04	−40.24	0.90 ± 0.05	−23.07
2	10^{-4}	−	1.21 ± 0.12	+47.56	0.56 ± 0.05	−52.13
	10^{-5}	−	1.04 ± 0.10	+26.82	0.87 ± 0.01	−25.64
	10^{-6}	−	0.97 ± 0.16	+18.29	0.89 ± 0.01	−23.93
3	10^{-4}	−	1.48 ± 0.10	+80.48	1.39 ± 0.94	+18.80
	10^{-5}	−	0.62 ± 0.07	−24.39	0.89 ± 0.01	−23.93
	10^{-6}	−	0.65 ± 0.02	−20.73	0.90 ± 0.05	−23.07
4	10^{-4}	−	0.72 ± 0.01	−12.19	0.74 ± 0.11	−36.75
	10^{-5}	−	0.81 ± 0.01	−1.21	0.91 ± 0.04	−22.22
	10^{-6}	+	1.02 ± 0.07	+24.39	0.82 ± 0.09	−29.91
5	10^{-4}	+	1.38 ± 0.12	+97.14	0.71 ± 0.16	+1.42
	10^{-5}	+	0.70 ± 0.09	0.00	0.76 ± 0.32	+8.57
	10^{-6}	−	0.55 ± 0.02	−21.42	0.91 ± 0.15	+30.00
6	10^{-4}	+	0.93 ± 0.10	+13.41	1.15 ± 0.12	−1.70
	10^{-5}	−	0.84 ± 0.06	+2.43	0.90 ± 0.28	−23.07
	10^{-6}	−	0.92 ± 0.03	+12.19	1.26 ± 0.45	+7.69
7	10^{-4}	−	1.08 ± 0.04	−10.00	1.31 ± 0.03	−9.16
	10^{-5}	−	1.47 ± 0.02	+22.50	1.11 ± 0.04	−7.50
	10^{-6}	+	1.13 ± 0.06	−5.83	0.97 ± 0.01	−19.16
8	10^{-4}	+	1.56 ± 0.17	+90.24	1.32 ± 0.18	+12.82
	10^{-5}	−	0.95 ± 0.03	+15.85	1.16 ± 0.16	−0.85
	10^{-6}	−	1.44 ± 0.18	+75.60	1.35 ± 0.08	+15.38
9	**10^{-4}**	−	0.67 ± 0.08	**−29.47**	0.64 ± 0.04	**−32.63**
	10^{-5}	−	0.52 ± 0.02	**−45.26**	0.47 ± 0.03	**−50.52**
	10^{-6}	−	0.67 ± 0.04	**−29.47**	0.81 ± 0.08	**−14.73**
10	**10^{-4}**	−	0.79 ± 0.03	**−16.84**	0.81 ± 0.08	**−14.73**
	10^{-5}	−	0.81 ± 0.04	**−14.73**	0.70 ± 0.13	**−26.31**
	10^{-6}	−	0.76 ± 0.06	**−20.00**	0.79 ± 0.03	**−16.84**
11	10^{-4}	+	0.84 ± 0.06	+2.43	1.35 ± 0.18	+15.38
	10^{-5}	−	1.34 ± 0.14	+63.41	1.13 ± 0.35	−3.41
	10^{-6}	−	1.11 ± 0.10	+35.36	1.38 ± 0.31	+17.94
12	**10^{-4}**	−	0.05 ± 0.01	**−93.90**	0.84 ± 0.09	−28.20
	10^{-5}	−	0.05 ± 0.01	**−95.12**	2.27 ± 0.11	**−94.01**
	10^{-6}	−	0.05 ± 0.01	**−93.90**	0.87 ± 0.03	−25.64
13	**10^{-4}**	−	0.04 ± 0.01	**−95.12**	0.47 ± 0.12	**−36.75**
	10^{-5}	−	0.04 ± 0.01	**−95.12**	1.74 ± 0.16	+48.71
	10^{-6}	−	0.04 ± 0.01	**−95.12**	1.08 ± 0.13	−7.69
14	**10^{-4}**	+	0.04 ± 0.02	**−95.12**	1.60 ± 0.16	+36.75
	10^{-5}	+	0.05 ± 0.01	**−93.90**	1.18 ± 0.02	+0.85
	10^{-6}	−	0.05 ± 0.03	**−93.90**	0.88 ± 0.05	−24.78
15	10^{-4}	−	1.19 ± 0.09	+70.00	0.68 ± 0.41	−2.85
	10^{-5}	−	1.01 ± 0.06	+44.28	0.77 ± 0.34	+10.00
	10^{-6}	−	0.79 ± 0.20	+12.85	0.78 ± 0.19	+11.42
16	10^{-4}	−	1.22 ± 0.34	+48.78	0.99 ± 0.30	−15.38
	10^{-5}	−	0.84 ± 0.07	+2.43	1.60 ± 0.45	+36.75
	10^{-6}	−	0.81 ± 0.05	−1.21	1.48 ± 0.04	+26.49
17	**10^{-4}**	−	0.92 ± 0.18	**−3.15**	0.80 ± 0.10	**−15.79**
	10^{-5}	−	0.76 ± 0.08	**−20.00**	0.76 ± 0.04	**−20.00**
	10^{-6}	−	0.80 ± 0.15	**−15.79**	0.80 ± 0.03	**−15.79**
18	**10^{-4}**	−	0.73 ± 0.13	**−23.15**	0.79 ± 0.10	**−16.84**
	10^{-5}	−	0.70 ± 0.05	**−26.31**	0.81 ± 0.11	**−14.73**
	10^{-6}	−	0.82 ± 0.16	**−13.68**	0.62 ± 0.08	**−34.73**
19	10^{-4}	+	1.43 ± 0.07	+19.16	1.03 ± 0.06	−14.16
	10^{-5}	−	1.33 ± 0.06	+10.83	0.91 ± 0.07	−24.16
	10^{-6}	+	0.99 ± 0.09	−17.50	0.95 ± 0.05	−20.83
20	10^{-4}	−	0.89 ± 0.01	+27.14	0.69 ± 0.30	−11.42
	10^{-5}	−	0.48 ± 0.08	−31.42	0.56 ± 0.08	−50.00
	10^{-6}	−	0.55 ± 0.21	−21.42	0.63 ± 0.17	−8.57
21	10^{-4}	+	0.59 ± 0.23	−15.74	0.65 ± 0.10	−7.14
	10^{-5}	+	0.56 ± 0.18	−20.00	0.55 ± 0.17	−21.42
	10^{-6}	+	0.85 ± 0.06	+21.42	0.56 ± 0.07	−20.00
22	10^{-4}	−	0.75 ± 0.29	+7.14	0.85 ± 0.06	+21.42
	10^{-5}	−	0.51 ± 0.19	−27.14	0.79 ± 0.32	+12.85
	10^{-6}	−	0.65 ± 0.21	−7.14	0.99 ± 0.03	+41.42
23	10^{-4}	−	0.74 ± 0.28	+5.71	0.81 ± 0.37	+15.71
	10^{-5}	−	0.75 ± 0.25	+7.14	0.90 ± 0.08	+28.57
	10^{-6}	−	0.74 ± 0.28	+5.71	0.89 ± 0.01	+27.14
24	10^{-4}	+	0.38 ± 0.12	−45.71	0.53 ± 0.17	−24.28
	10^{-5}	+	0.44 ± 0.13	−37.14	0.71 ± 0.14	+1.42
	10^{-6}	+	0.60 ± 0.10	−14.28	0.69 ± 0.28	−1.42
25	10^{-4}	−	0.54 ± 0.20	−22.85	0.62 ± 0.24	−11.42

Table 1 (*continued*)

Entry	Conc.(M)	Cytotoxicity	ConA Mean + SE	ConA-induced T cell proliferation rate (%)	LPS mean + SE	LPS-induced B cell proliferation rate (%)
	10^{-5}	−	0.49 ± 0.11	−30.00	0.48 ± 0.09	−31.42
	10^{-6}	−	0.65 ± 0.15	−7.14	1.14 ± 0.36	+62.85
26	10^{-4}	+	0.63 ± 0.28	−10.00	0.79 ± 0.37	+12.85
	10^{-5}	+	0.36 ± 0.04	−48.57	0.58 ± 0.17	−17.14
	10^{-6}	−	0.91 ± 0.15	+30.00	0.89 ± 0.14	+27.14
27	10^{-4}	−	1.23 ± 0.09	+2.50	0.99 ± 0.02	−17.50
	10^{-5}	−	1.20 ± 0.05	0.00	1.00 ± 0.01	−16.66
	10^{-6}	+	1.03 ± 0.06	−14.16	0.91 ± 0.02	−24.16
28	10^{-4}	−	0.76 ± 0.26	+8.57	1.23 ± 0.22	+75.71
	10^{-5}	−	0.79 ± 0.20	+12.85	0.64 ± 0.11	−8.57
	10^{-6}	+	0.50 ± 0.14	−28.57	1.02 ± 0.03	+45.71
29	**10^{-4}**	−	0.95 ± 0.05	**−20.83**	0.78 ± 0.01	**−35.00**
	10^{-5}	−	1.12 ± 0.14	**−6.66**	0.93 ± 0.01	**−22.50**
	10^{-6}	−	1.13 ± 0.04	**−5.83**	0.91 ± 0.04	**−24.16**
30	**10^{-4}**	−	0.89 ± 0.13	**−6.31**	0.87 ± 0.11	**−8.42**
	10^{-5}	−	0.67 ± 0.08	**−29.47**	0.60 ± 0.06	**−36.84**
	10^{-6}	−	0.68 ± 0.05	**−28.42**	0.53 ± 0.04	**−44.21**
31	10^{-4}	+	1.53 ± 0.05	+27.50	1.40 ± 0.02	+16.66
	10^{-5}	−	1.36 ± 0.04	+13.33	1.02 ± 0.01	−15.00
	10^{-6}	+	0.96 ± 0.06	−20.00	0.90 ± 0.01	−25.00

+ Indicate immune stimulant agents while − indicate immunosuppressive agents. Results are mean standard error (SE) of three separate experiments, conducted in triplicate at the concentrations 1×10^{-4}, 1×10^{-5} and 1×10^{-6} M.
The bold values are shown for those compounds which have proved to be active and those in normal font represent least significant.

was cytotoxic. Cytotoxic compounds **19**, **20** and **21** showed inhibition against LPS induced B-cell proliferation but not against ConA. Compounds **22**–**24** and **27** proved to be ineffective in inhibiting the Con A and LPS induced cell proliferation effect. In terms of SAR, no clear relationship could be established.

3. Conclusion

We have demonstrated the inhibitory activity of a novel library of 1,2,3-triazole desmotroposantonin derivatives created through Azide–Alkyne Huisgen 1,3-dipolar cycloaddition reaction and characterized by spectral analysis against ConA induced T-cell and LPS induced B-cell proliferation. Six (**9**, **10**, **17**, **18**, **29**, and **30**) out of a library of 31 compounds have been identified as potent immunosuppressant agents showing inhibition against induced T-cell and B-cell proliferation and the bioactives found without any cytotoxic effect. Further, selective diminutive effect against ConA induced T-cell proliferation for compounds **12** and **13** have also been demonstrated.

4. Experimental

4.1. Chemistry

All reagents for chemical synthesis were obtained from Sigma Aldrich and the solvents used in reactions were distilled and dried prior to use. All the chemical reactions were monitored by TLC on 0.25 mm silica gel 60 F_{254} plates (E. Merck) using 2% ceric ammonium sulphate solution for detection of the spots. Purification of compounds was carried out by column chromatography using Silica gel 60–120 mesh stationary phase. ^{1}H NMR and ^{13}C NMR spectra (with chemical shifts expressed in δ and coupling constants in Hertz) were recorded on Bruker DPX 200, 400 and DPX 500 instruments using $CDCl_3$ or CD_3OD as the solvents with TMS as internal standard. High resolution mass spectra (HRMS) were recorded on Agilent Technologies 6540 instrument and IR recorded on an FT-IR Bruker (270-30) spectrophotometer. Melting points of compounds were recorded on Buchi melting point apparatus B-542. HPLC was run on Agilent Technologies 1200 series instrument. All the compounds (**1**–**31**) were >95% purity as confirmed by HPLC analysis (RP-18 column, Merck, with UV detector, isocratic mobile phase acetonitrile and water (70:30) with flow rate 0.8 mL/min).

4.1.1. Isolation of α-santonin

α-Santonin was isolated in bulk quantity from the aerial part of *A. laciniata* (duly authenticated by the taxonomist of our institute). α-Santonin used in present study was of 98% purity (HPLC analysis) achieved through repeated column chromatography over silica gel 60–120 mesh and the natural product was well characterized by spectroscopic study (found in agreement with the literature data) [32].

4.1.2. Preparation of α-desmotroposantonin acetate (**2**)

The title compound was prepared by the Thiele acetylation (dienone-phenol rearrangement) method [32], by treating α-santonin (1.0 g, 4 mmol) the acetic anhydride (5 mL) and sulphuric acid (0.5 mL, 9.3 mmol) at 0–10 °C temperature for 1 h. On usual workup, the acetylated product **2** (1.04 g, 89% yield) was obtained as a solid, mp 139.5–139.9 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83 (1H, s, Ar–*H*), 5.58 (1H, d, J = 6.0 Hz, Ar–C*H*O–), 2.73–2.77 (1H, m, –CHC*H*CH_3), 2.54–2.56 (2H, m, Ar–CH_2–), 2.42–2.44 (1H, m, –C*H*$CHCH_3$), 2.33 (3H, s, –OCOCH_3), 2.22 and 2.21 (3H each, s, 2× Ar–CH_3), 1.93–1.73 (2H, m, $ArCH_2CH_2$–), 1.39 (3H, d, J = 7.2 Hz, –CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.45, 169.62, 147.41, 134.82, 134.09, 131.27, 129.01, 123.84, 75.47, 41.60, 40.43, 24.01, 23.36, 20.78, 19.53, 14.45, 12.09. IR γ_{max} (neat): 2925, 1766, 1465, 1213, 987, 950, 908, 696, 669 cm^{-1}. HRMS m/z calcd for $C_{17}H_{20}O_4$ $[M + H]^+$ 289.14343, found. 289.14271.

4.1.3. Preparation of α-desmotroposantonin (**3**)

The title compound was prepared in (0.785 g, 92% yield) by deacetylation of α-desmotroposantonin acetate (**2**) (1.0 g) using methanol/ammonium hydroxide (1:1) mixture (50 mL) with slight modification of the reported method [37], mp 197–199 °C, lit. mp 198 °C. ^{1}H NMR (200 MHz, CD_3OD): δ 6.65 (1H, s, Ar–*H*), 5.71 (1H, d, J = 6.08 Hz, Ar–C*H*O–), 2.61–2.70 (1H, m, –CHC*H*CH_3), 2.50–2.54 (2H, m, Ar–CH_2–), 2.37–2.46 (1H, m, –C*H*$CHCH_3$), 2.21 and 2.15 (3H each, s, 2× Ar–CH_3), 1.89 and 1.61 (1H each, m, $ArCH_2CH_2$–), 1.35 (3H, d, J = 7.29, –CHCH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 181.0, 153.02, 134.30, 130.61, 127.37, 123.22, 117.74, 76.71, 41.99, 40.87, 23.83, 23.68, 19.5, 14.47, 11.48. IR γ_{max} (neat): 3426, 2925, 1761, 1464, 1171, 867, 814, 716, 688, 624 cm^{-1}. HRMS m/z calcd for $C_{15}H_{18}O_3$ $[M + H]^+$ 247.13287, found 247.13195.

*4.1.4. Preparation of O-propargyl-α-desmotroposantonin (**4**)*

The compound prepared by the propargylation of compound **3** (1.0 g, 4 mmol), using the propargyl bromide (0.68 mL, 6 mmol) and K_2CO_3 (0.5 g, 8 mmol) in acetone (50 mL) under reflux for 6 h to give after usual work the propargylated product **4** (1.10 g, 96% yield) [33] as a solid, mp 105–108 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85 (1H, s, Ar–*H*), 5.61 (1H, d, *J* = 6.2 Hz, Ar–C*H*O–), 4.68 (2H, s, –OCH_2–), 2.64–2.72 (1H, m, –CHC*H*CH_3), 2.39–2.58 (4H, m, Ar–CH_2–, –C*H*CHCH_3, –OCH$_2$C*H*–), 2.29 and 2.25 (3H each, s, 2× Ar–CH_3), 1.81–1.93 and 1.68–1.80 (1H each, m, ArCH_2CH_2–), 1.39 (3H, d, *J* = 7.3 Hz, CH_3–CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.58, 153.89, 134.10, 131.04, 129.10, 126.57, 115.37, 79.02, 75.70, 75.23, 56.60, 41.82, 40.52, 23.74, 23.64, 19.98, 14.51, 11.67. IR γ_{max} (neat): 3528, 3279, 2929, 2359, 2119, 1765, 1597, 1479, 1378, 1295, 1223, 1165, 1115, 1051, 986 cm^{-1}. HRMS *m*/*z* calcd for $C_{18}H_{21}O_3$ $[M + H]^+$ 285.14852, found 285.14772.

*4.1.5. General experimental procedure for preparation 1,2,3-triazoles of α-desmotroposantonin (**5**–**31**)*

NaN_3 (1.2 equiv), $CuSO_4$ (0.1 equiv), and boronic acids (1.2 equiv) in methanol (10 mL) were allowed to react for 1–4 h, followed by addition of water (10 mL), sodium ascorbate (0.5 equiv), and propargylated α-desmotroposantonin (1.0 equiv) [34]. The contents were stirred vigorously at room temperature for 2–8 h (as monitored by TLC analysis). After completion of the reaction, the contents diluted with water and extracted with ethyl acetate (3 times). The combined ethyl acetate extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure on a rota vapour. The crude product obtained thus subjected was put to column chromatography (silica gel) with EtOAc:Hexane (15:85) mixture as eluent to afford the desired pure products in >97% yields.

*4.1.5.1. Synthesis of {(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**5**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (100 mg, 0.35 mmol) and phenyl boronic acid (51.2 mg, 0.42 mmol) as per the method described in Section 4.1.5 to give **5** (137 mg, 97% yield), brown solid; mp: 182–183 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (1H, s, –NC*H*–), 7.76 (2H, d, *J* = 7.17 Hz, Ar^1–*H*), 7.45–7.58 (3H, m, Ar^1–*H*), 6.91 (1H, s, Ar–*H*), 5.63 (1H, d, *J* = 6.29 Hz, Ar–C*H*O–), 5.30 (2H, s, –OCH_2–), 2.68–2.78 (1H, m, –CHC*H*CH_3), 2.58–2.68 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.32 and 2.25 (3H each, s, 2× Ar–CH_3), 1.75–1.91 and 1.58–1.66 (1H each, m, Ar–CH$_2$CH_2–), 1.39 (3H, d, *J* = 7.28 Hz, CH_3CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.58, 154.46, 145.82, 137.03, 134.35, 131.05, 129.79 (3CH), 128.86 (2CH), 128.80, 126.11, 120.63, 115.10, 75.74, 62.91, 41.82, 40.48, 23.69, 23.64, 19.97, 14.50, 11.73. IR γ_{max} (neat): 3720, 2921, 1596, 1499, 1301, 1228, 1168, 1045, 947, 851, 766, 681, 489, 450 cm^{-1}. HRMS *m*/*z* calcd for $C_{24}H_{25}N_3O_3$ $[M + H]^+$ 404.19686, found 404.19786.

*4.1.5.2. Synthesis of 2-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-naphthalene (**6**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (85 mg, 0.30 mmol) and naphthalen-2-yl-2-boronic acid (62 mg, 0.36 mmol) as per method described in Section 4.1.5 to give **6** (130 mg, 96% yield). Yellow gummy mass; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.17 (2H, d, *J* = 6.65 Hz, Ar^1–*H*), 7.90–8.10 (4H, m, 3× Ar^1–*H* and –NC*H*–), 7.56–7.60 (2H, dd, *J* = 8.77 and 4.08 Hz, Ar^1–*H*), 6.92 (1H, s, Ar–*H*), 5.63 (1H, d, *J* = 6.14 Hz, Ar–C*H*O–), 5.33 (2H, s, –OCH_2–), 2.63–2.71 (1H, m, –CHC*H*CH_3), 2.53–1.59 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.31 and 2.25 (3H each, s, 2× Ar–CH_3), 1.75–1.90 and 1.57–1.69 (1H each, m, Ar–CH$_2$CH_2–), 1.39 (3H, d, *J* = 7.32 Hz, CH_3CH–). ^{13}C NMR (125 MHz): δ 179.60, 154.47, 145.64, 134.37, 133.22, 132.94, 131.05, 130.06, 130.04, 128.78, 128.31, 127.95, 127.49, 127.0, 126.12, 120.79, 118.97, 118.57, 115.07, 75.75, 62.97, 41.84, 40.48, 23.70, 23.65, 20.0, 14.51, 11.79. IR γ_{max} (neat): 3400, 2926, 2853, 2107, 1767, 1633, 1602, 1515, 1444, 1381, 1297, 1222, 1164, 1124, 1044, 987, 950, 857, 814, 771, 669 cm^{-1}. HRMS *m*/*z* calcd for $C_{28}H_{27}N_3O_3$ $[M + H]^+$ 454.21251, found 454.21143.

*4.1.5.3. Synthesis of 3-hydroxy-1-{(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}-benzene (**7**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (114 mg, 0.40 mmol) and 3-hydroxy phenyl boronic acid (66 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **7** (111 mg, 98% yield). Yellow solid; mp: 192–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (1H, s, –NC*H*–), 7.31–7.40 (3H, m, Ar^1–*H*), 7.10 (1H, s, Ar–*H*), 6.88 (1H, d, *J* = 8.0 Hz, Ar^1–*H*), 5.69 (1H, d, *J* = 6.0 Hz, Ar–C*H*O–), 5.19 (2H, s, –OCH_2–), 2.66–2.71 (1H, m, –CHC*H*CH_3), 2.42–2.53 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.44 and 2.22 (3H each, s, 2× Ar–CH_3), 1.83–1.88 and 1.51–1.55 (1H each, m, Ar–CH$_2$CH_2–), 1.29 (3H, d, *J* = 7.21 Hz, CH_3CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.19, 158.73, 154.26, 144.69, 137.84, 134.50, 131.32, 131.26, 129.32, 125.28, 122.81, 116.28, 115.46, 111.05, 107.44, 75.82, 62.04, 41.09, 40.57, 23.51, 23.48, 19.82, 14.43, 11.76. IR γ_{max} (neat): 2928, 1763, 1598, 1473, 1228, 1167, 1116, 992, 864, 835, 734, 694 cm^{-1} HRMS *m*/*z* calcd for $C_{24}H_{25}N_3O_4$ $[M + H]^+$ 420.19178, found 420.1912.

*4.1.5.4. Synthesis of 3,4-dimethoxy-1{(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}-benzene (**8**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (71 mg, 0.25 mmol) and 3,4-dimethoxy phenyl boronic acid (54.6 mg, 0.30 mmol) as per method described in Section 4.1.5 to give **8** (112 mg, 97% yield). Yellow solid; mp: 144–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (1H, s, –NC*H*–), 7.29 (1H, d, *J* = 2.38 Hz, Ar^1–*H*), 7.10 (1H, dd, *J* = 8.61 and 2.44 Hz, Ar^1–*H*), 6.87 (1H, d, *J* = 8.62 Hz, Ar^1–*H*), 6.83 (1H, s, Ar–*H*), 5.54 (1H, d, *J* = 6.27 Hz, Ar–C*H*O–), 5.20 (2H, s, –OCH_2–), 3.88 and 3.86 (3H each, s, 2× –OCH_3), 2.62–2.66 (1H, m, –CHC*H*CH_3), 2.34–2.48 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.23 and 2.16 (3H each, s, 2× Ar–CH_3), 1.78–1.88 and 1.60–1.69 (1H each, m, Ar–CH$_2$CH_2–), 1.31 (3H, d, *J* = 7.16 Hz, CH_3CH–). ^{13}C NMR (100 MHz): δ 179.59, 154.48, 149.80, 149.49, 145.31, 134.35, 131.02, 130.61, 128.76, 126.09, 120.92, 115.10, 112.59, 111.22, 105.09, 75.74, 62.95, 56.27, 56.21, 41.82, 40.49, 23.70, 23.64, 19.98, 14.51, 11.74. IR γ_{max} (neat): 3399, 2929, 1764, 1602, 1519, 1459, 1382, 1298, 1262, 1238, 1164, 1123, 1045, 1024, 949, 849, 769, 668 cm^{-1}. HRMS *m*/*z* calcd for $C_{26}H_{29}N_3O_5$ $[M + H]^+$ 464.21799, found 464.21746.

*4.1.5.5. Synthesis of 3,4-methylenedioxy-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**9**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (113.7 mg, 0.40 mmol) and 3,4-methylenedioxy phenyl boronic acid (80 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **9** (173 mg, 97% yield). Brown solid; mp: 215–235 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (1H, s, NC*H*–), 7.06 (1H, dd, *J* = 8.31 and 2.16 Hz, Ar^1–*H*), 6.83 (1H, s, Ar–*H*), 6.81 (1H, d, *J* = 8.16 Hz, Ar^1–*H*), 6.01 (2H, s, –OCH_2O–), 5.55 (1H, d, *J* = 6.23 Hz, Ar–C*H*O–), 5.20 (2H, s, –OCH_2–), 2.64–2.68 (1H, m, –CHC*H*CH_3), 2.37–2.51 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.24 and 2.18 (3H each, s, 2× Ar–CH_3), 1.85–1.95 and 1.62.1.71 (1H each, m, ArCH_2CH_2–), 1.31 (3H, d, *J* = 7.35 Hz, CH_3CH–). ^{13}C NMR (125 MHz): δ 179.66, 154.31, 148.65, 148.11, 145.33, 134.37, 131.49, 131.02, 128.77, 126.08, 120.96, 115.03, 114.37, 108.53, 102.87, 102.14, 75.76, 62.91, 41.83, 40.48, 23.70, 23.63, 20.10, 14.52, 11.76. IR γ_{max} (neat): 3300, 2922, 1763, 1600, 1462, 1381, 1122, 1039, 944, 879, 830, 745, 698, 647, 512 cm^{-1}. HRMS *m*/*z* calcd for $C_{25}H_{25}N_3O_5$ $[M + H]^+$ 448.18669, found 448.18682.

*4.1.5.6. Synthesis of 3,4,5-trimethoxy-1-(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}-benzene (**10**).* The title compound

prepared by the reaction of propargylated α-desmotroposantonin (57 mg, 0.20 mmol) and 3,4,5-trimethoxy phenyl boronic acid (51 mg, 0.24 mmol) as per method described in Section 4.1.5 to give **10** (96 mg, 97% yield). Brown solid; mp: 207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, s, NC*H*−), 6.96 (2H, s, Ar^1−*H*), 6.91 (1H, s, Ar−*H*), 5.63 (1H, d, *J* = 6.14 Hz, Ar−C*H*O−), 5.28 (2H, s, −OCH_2−), 3.94 (6H, s, 2× −OCH_3), 3.89 (3H, s, −OCH_3), 2.66–2.70 (1H, m, −CHC*H*CH$_3$), 2.39–2.53 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.32 and 2.25 (3H each, s, 2× Ar−CH_3), 1.84–193 and 1.71–1.80 (1H each, m, ArCH$_2$CH_2−), 1.39 (3H, d, *J* = 7.31 Hz, CH_3CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.58, 154.48, 153.92 (2C), 145.35, 138.44, 134.34, 132.85, 131.02, 128.80, 126.03, 121.12, 115.09, 98.63 (2CH), 75.73, 62.86, 61.01, 56.49 (2CH$_3$), 41.79, 40.51, 23.69, 22.6, 19.95, 14.49, 11.71. IR γ_{max} (neat): 3404, 2919, 1763, 1603, 1462, 1127, 827, 722, 699, 646, 521 cm^{-1}. HRMS *m*/*z* calcd for $C_{27}H_{31}N_3O_6$ [M + H]$^+$ 494.22856, 494.22772.

*4.1.5.7. Synthesis of 4-pheny-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**11**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (100 mg, 0.35 mmol) and biphenyl boronic acid (83 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **11** (162 mg, 97% yield). Yellow solid; mp: 186–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (1H, s, −NC*H*−), 7.75 (2H, d, *J* = 8.80 Hz, 2× Ar^1−*H*), 7.67 (2H, dd, *J* = 8.40 and 1.60 Hz, 2× Ar^1−*H*), 7.55 (2H, dd, *J* = 8.40 and 1.20 Hz, 2× Ar^2−*H*), 7.37 (3H, m, 3× Ar^2−*H*), 6.84 (1H, s, Ar−*H*), 5.55 (1H, d, *J* = 6.40 Hz, Ar−C*H*O−), 5.23 (2H, s, −OCH_2−), 2.63–2.67 (1H, m, −CHC*H*CH$_3$), 2.41–2.55 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.46 and 2.25 (3H each, s, 2× Ar−CH_3), 1.80–1.90 and 1.60–1.69 (1H each, m, Ar−CH$_2$CH_2−), 1.32 (3H, d, *J* = 7.41 Hz, CH_3CH−). ^{13}C NMR (100 MHz $CDCl_3$): δ 179.63, 154.44, 141.87, 139.59, 139.26 (2C), 134.37, 131.04, 128.99 (2CH), 128.79, 128.38 (2CH), 127.98, 127.08 (2CH), 126.12, 120.91 (3CH), 115.09, 75.77, 62.91, 41.84, 40.49, 23.70, 23.64, 19.99, 14.50, 11.76. IR γ_{max} (neat): 3391, 2926, 2853, 1766, 1599, 1525, 1488, 1458, 1407, 1381, 1351, 1318, 1298, 1223, 1203, 1165, 1124, 1088, 1046, 949, 932, 904, 842, 720, 698, 666, 555, 508 cm^{-1}. HRMS *m*/*z* calcd for $C_{30}H_{29}N_3O_3$ [M + H]$^+$ 480.22816, found 480.22678.

*4.1.5.8. Synthesis of 6-methoxy-2-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-naphthalene (**12**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (71 mg, 0.25 mmol) and 6-methoxy naphthalen-2-yl-2-boronic acid (61 mg, 0.30 mmol) as per method described in Section 4.1.5 to give **12** (117 mg, 97% yield). Yellow solid; mp: 230 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (2H, s and d merged, *J* = 8.32 Hz, Ar^1−*H*), 7.90 (1H, s, −NC*H*−), 7.84 (2H, s and d merged, *J* = 8.36 Hz, Ar^1−*H*), 7.22 (2H, d merged, *J* = 8.32 Hz, Ar^1−*H*), 6.91 (1H, s, Ar−*H*), 5.59 (1H, d, *J* = 5.77 Hz, Ar−C*H*O−), 5.31 (2H, s, −OCH_2−), 3.94 (3H, s, OCH_3), 2.60–2.64 (1H, m, −CHC*H*CH$_3$), 2.35–2.49 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.32 and 2.23 (3H each, s, 2× Ar−CH_3), 1.83–1.93 and 1.65–1.75 (1H each, m, Ar−CH$_2$CH_2−), 1.38 (3H, d, *J* = 7.23 Hz, CH_3CH−). ^{13}C NMR (100 MHz $CDCl_3$): δ 179.70, 158.54, 154.44, 145.44, 134.34, 134.32, 132.61, 130.97, 129.70, 128.75, 128.56, 128.48, 126.08, 120.82, 120.44, 119.50, 118.66, 115.07, 105.83, 75.86, 75.28, 62.52, 55.23, 41.12, 40.29, 23.67, 23.62, 14.47, 11.74. IR γ_{max} (neat): 3400, 2917, 2849, 1764, 1608, 1514, 1462, 1419, 1383, 1298, 1265, 1222, 1164, 1123, 1047, 1027, 985, 949, 932, 909, 853, 817, 706, 666, 540, 506 cm^{-1}. HRMS *m*/*z* calcd for $C_{29}H_{29}N_3O_4$ [M + H]$^+$ 484.22254, found 484.22192.

*4.1.5.9. Synthesis of β-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-styrene (**13**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (85 mg, 0.30 mmol) and (*E*)-2-phenyl vinyl boronic acid (53 mg, 0.36 mmol) as per method described in Section 4.1.5 to give **13** (123 mg, 96% yield). Yellow solid; mp: 168 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (1H, s, −NC*H*−), 7.76 (1H, d, *J* = 14.73 Hz, −NC*H*═CH−), 7.34–7.5 (5H, m, Ar^1−*H*), 7.21 (1H, d, *J* = 14.75 Hz, −NCH═C*H*−), 6.87 (1H, s, Ar−*H*), 5.62 (1H, d, *J* = 6.14 Hz, Ar−C*H*O−), 5.26 (2H, s, −OCH_2−), 2.70–2.74 (1H, m, −CHC*H*CH$_3$), 2.45–2.59 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.32 and 2.24 (3H each, s, 2× Ar−CH_3), 1.79–1.89 and 1.65–1.74 (1H each, m, Ar−CH$_2$CH_2−), 1.39 (3H, d, *J* = 7.31 Hz, CH_3CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.65, 154.36, 145.24, 134.35, 133.49, 131.04, 129.03 (2CH), 128.86, 128.77, 126.77 (2CH), 126.05, 122.91, 122.11, 119.87, 114.95, 75.76, 62.79, 41.83, 40.48, 23.69, 23.64, 19.98, 14.51, 11.74. IR γ_{max} (neat): 3391, 2918, 2850, 1765, 1657, 1599, 1481, 1455, 1351, 1297, 1223, 1203, 1165, 1124, 1045, 986, 949, 903, 846, 752, 693, 666, 582, 548, 526, 520, 513, 507 cm^{-1}. HRMS *m*/*z* calcd for $C_{26}H_{27}N_3O_3$ [M + H]$^+$ 430.21251, found 430.21208.

*4.1.5.10. Synthesis of 3-nitro-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**14**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (114 mg, 0.40 mmol) and 3-nitro phenyl boronic acid (80 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **14** (170 mg, 95% yield). Yellow solid; mp: 199–201 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.64 (1H, d, *J* = 1.83 Hz, Ar^1−*H*), 8.32 (1H, d, *J* = 8.06 Hz, Ar^1−*H*), 8.19 (1H, d, *J* = 8.18 Hz, Ar^1−*H*), 8.16 (1H, s, −NC*H*−), 7.76 (1H, dd, *J* = 8.20 and 8.19 Hz, Ar^1−*H*), 6.19 (1H, s, Ar−*H*), 5.63 (1H, d, *J* = 6.19 Hz, Ar−C*H*O−), 5.33 (2H, s, −OCH_2−), 2.67–2.71 (1H, m, −CHC*H*CH$_3$), 2.45–2.59 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.35 and 2.25 (3H each, s, 2× Ar−CH_3), 1.81–1.91 and 1.62–1.71 (1H each, m, Ar−CH$_2$CH_2−), 1.39 (3H, d, *J* = 7.31 Hz, CH_3CH−). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.64, 154.22, 148.91, 146.31, 137.66, 134.42, 131.08, 131.02, 128.97, 126.07, 125.99, 123.28, 120.60, 115.40, 114.94, 75.70, 62.69, 41.77, 40.48, 23.69, 23.60, 20.02, 14.51, 11.75. IR γ_{max} (neat): 3435, 2925, 1764, 1597, 1535, 1482, 1382, 1350, 1298, 1222, 1165, 1125, 1045, 986, 950, 903, 871, 804, 759, 738, 667 cm^{-1}. HRMS *m*/*z* calcd for $C_{24}H_{24}N_4O_5$ [M + H]$^+$ 449.18194, found 449.18095.

*4.1.5.11. Synthesis of 4-fluoro-1{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**15**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (100 mg, 0.35 mmol) and 4-fluoro phenyl boronic acid (59 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **15** (144 mg, 98% yield). Yellow solid; mp: 186–190 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98 (1H, s, −NC*H*−), 7.73 (2H, d, *J* = 8.78 Hz, Ar^1−*H*), 7.24 (2H, d, *J* = 8.74 Hz, Ar^1−*H*), 6.90 (1H, s, Ar−*H*), 5.62 (1H, d, *J* = 6.13 Hz, Ar−C*H*O−), 5.29 (2H, s, −OCH_2−), 2.64–2.68 (1H, m, −CHC*H*CH$_3$), 2.45–2.59 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.31 and 2.25 (3H each, s, 2× Ar−CH_3), 1.81–1.91 and 1.63–1.72 (1H each, m, Ar−CH$_2$CH_2−), 1.38 (3H, d, *J* = 7.27 Hz, CH_3CH−). ^{13}C NMR (125 MHz): δ 179.67, 162.12 ($^3J_{CF}$ = 251.69 Hz), 154.35, 145.21, 134.39, 131.03, 128.82, 126.06, 122.68, 122.65 ($^3J_{CF}$ = 8.68 Hz), 120.82, 116.76 ($^2J_{CF}$ = 23.27 Hz), 115.0, 75.75, 62.86, 41.79, 40.46, 23.67, 23.60, 20.01, 14.51, 11.76. IR γ_{max} (neat): 3456, 2919, 1763, 1515, 1461, 1174, 1110, 846, 788, 702, 627, 550, 479 cm^{-1}. HRMS *m*/*z* calcd for $C_{24}H_{24}FN_3O_3$ [M + H]$^+$ 422.18744, found 422.18657.

*4.1.5.12. Synthesis of 4-bromo-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**16**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (71 mg, 0.25 mmol) and 4-bromo phenyl boronic acid (60 mg, 0.30 mmol) as per method described in Section 4.1.5 to give **16** (116 mg, 97% yield). Yellow solid; mp: 217–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, s, −NC*H*−), 7.62–7.67 (4H, m, 4× Ar^1−*H*), 6.88 (1H, s, Ar−*H*), 5.62 (1H, s, *J* = 6.01 Hz, Ar−C*H*O−), 5.28 (2H, s, −OCH_2−), 2.67–2.71 (1H, m, −CHC*H*CH$_3$), 2.42–2.56 (3H, m, Ar−CH_2−, −C*H*CHCH$_3$), 2.30 and 2.23 (3H each, s, 2× Ar−CH_3), 1.82–1.92 and 1.67–1.76 (1H each, m, Ar−CH$_2$CH_2−), 1.39 (3H, d, *J* = 7.27 Hz, CH_3CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.67, 154.37, 145.83, 137.03, 134.41, 132.97 (2CH), 131.40, 131.08, 128.89, 126.12, 122.04

(2CH), 120.53, 115.08, 75.78, 62.86, 41.83, 40.48, 23.69, 23.63, 19.98, 14.51, 11.75. IR γ_{max} (neat): 3368, 2925, 2124, 1759, 1586, 1558, 1497, 1427, 1392, 1369, 1349, 1305, 1230, 1175, 1124, 1102, 1079, 1063, 1010, 987, 949, 825, 769, 735, 681, 627, 547, 517 cm^{-1}. HRMS *m/z* calcd for $C_{24}H_{24}BrN_3O_3$ $[M + H]^+$ 482.10738, found 482.10591.

*4.1.5.13. Synthesis of 3-iodo-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**17**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (58 mg, 0.20 mmol) and 3-iodo phenyl boronic acid (60 mg, 0.24 mmol) as per method described in Section 4.1.5 to give **17** (103 mg, 98% yield). Colourless solid; mp: 179–184 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.01 (1H, d, *J* = 8.36 Hz, Ar^1–*H*), 7.89 (1H, s, –NC*H*–), 7.46–7.52 (2H, m, 2× Ar^1–*H*), 7.26–7.29 (1H, m, Ar^1–*H*), 6.92 (1H, s, Ar–*H*), 5.61 (1H, d, *J* = 6.06 Hz, Ar–C*H*O–), 5.33 (2H, s, –OCH_2–), 2.65–2.69 (1H, m, –CHC*H*CH_3), 2.47–2.61 (3H, m, Ar–CH_2–, –*CH*CH_3), 2.30 and 2.25 (3H each, s, 2× Ar–CH_3), 1.80–1.90 and 1.60–1.69 (1H each, m, $ArCH_2CH_2$–), 1.39 (3H, d, *J* = 7.32 Hz, CH_3CH–). ^{13}C NMR (100 MHz $CDCl_3$): δ 179.53, 154.45, 144.64, 140.28, 140.04, 134.32, 131.54, 131.03, 129.28, 128.88, 127.91, 126.36, 124.56, 115.55, 93.95, 75.73, 63.13, 41.85, 40.52, 23.74, 23.69, 20.0, 14.54, 11.78. IR γ_{max} (neat): 3404, 2923, 1766, 1483, 1378, 1297, 1223, 1166, 1089, 1011, 987, 855, 706, 630 cm^{-1}. HRMS *m/z* calcd for $C_{24}H_{24}IN_3O_3$ $[M + H]^+$ 530.09351, found 530.09318.

*4.1.5.14. Synthesis of 5-iodo-2-methyl-1-{(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}-benzene (**18**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (100 mg, 0.35 mmol) and 5-iodo-2-methyl phenyl boronic acid (110 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **18** (187 mg, 98% yield). Yellow solid; mp: 152–154 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (1H, s, NC*H*–), 7.74 (2H, dd, *J* = 7.85 and 1.69 Hz, Ar^1–*H*), 7.12 (1H, d, *J* = 7.78 Hz, Ar^1–*H*), 6.90 (1H, s, Ar–*H*), 5.62 (1H, d, *J* = 6.17 Hz, Ar–C*H*O–), 5.29 (2H, s, –OCH_2–), 2.65–2.69 (1H, m, –CHC*H*CH_3), 2.41–2.55 (3H, m, Ar–CH_2–, –*CH*CH_3), 2.31 and 2.25 (3H each, s, 2× Ar–CH_3), 2.05 (3H, s, Ar^1–CH_3), 1.82–1.91 and 1.66–1.75 (1H each, m, $ArCH_2CH_2$–), 1.39 (3H, d, *J* = 7.31, CH_3CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.56, 154.41, 144.83, 138.83, 137.38, 134.57, 134.33, 133.45, 133.04, 131.04, 128.87, 126.15, 123.88, 115.22, 90.06, 75.70, 62.98, 41.80, 40.47, 23.70, 23.63, 19.97, 17.67, 14.50, 11.72. IR γ_{max} (neat): 3711, 2926, 1767, 1594, 1482, 1379, 1298, 1225, 1165, 1120, 1044, 991, 946, 863, 827, 790, 733, 696, 658, 610 cm^{-1}. HRMS *m/z* calcd for $C_{25}H_{26}IN_3O_3$ $[M + H]^+$ 544.10916, found 544.10808.

*4.1.5.15. Synthesis of 2-fluoro-5-iodo-1-{(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}-benzene (**19**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (114 mg, 0.40 mmol) and 2-fluoro-6-iodo-phenyl boronic acid (128 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **19** (216 mg, 99% yield). Colourless solid; mp: 163–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (1H, d, *J* = 7.90 Hz, Ar^1–*H*), 7.70 (1H, s, –NC*H*–), 7.18–7.24 (2H, m, 2× Ar^1–*H*), 6.82 (1H, s, Ar–*H*), 5.54 (1H, d, *J* = 6.16 Hz, Ar–C*H*O–), 5.27 (2H, s, –OCH_2–), 2.59–2.63 (1H, m, –CHC*H*CH_3), 2.42–2.56 (3H, m, Ar–CH_2–, –*CH*CHCH_3), 2.28 and 2.17 (3H each, s, 2× Ar–CH_3), 1.78–1.88 and 1.61–1.70 (1H each, m, Ar–CH_2CH_2–), 1.32 (3H, d, *J* = 7.28 Hz, CH_3CH–). ^{13}C NMR (125 MHz $CDCl_3$): δ 179.65, 158.16 ($^1J_{CF}$ = 258.94 Hz), 154.35 ($^2J_{CF}$ = 19.24 Hz), 144.94, 135.28 ($^4J_{CF}$ = 3.90 Hz), 134.32, 133.12 ($^3J_{CF}$ = 7.92 Hz), 130.95, 129.53, 128.92, 126.34, 124.83, 116.91 ($^2J_{CF}$ = 19.87 Hz), 115.60, 96.99, 75.75, 63.21, 41.80, 40.52, 23.72, 23.63, 19.96, 14.51, 11.36. IR γ_{max} (neat): 3405, 2924, 1764, 1643, 1462, 1254, 1090, 952, 808, 700, 648, 529, 429 cm^{-1}. HRMS *m/z* calcd for $C_{24}H_{23}FIN_3O_3$ $[M + H]^+$ 548.08408, found 548.08447.

*4.1.5.16. Synthesis of 6-bromo-2-fluoro-3-iodo-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**20**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (129 mg, 0.45 mmol) and 6-bromo-2-fluoro-3-iodo phenyl boronic acid (186 mg, 0.54 mmol) as per method described in Section 4.1.5 to give **20** (272 mg, 97% yield). Yellow gummy mass. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (1H, d, *J* = 8.58, Ar^1–*H*), 7.79 (1H, s, –NC*H*–), 7.34 (1H, d, *J* = 8.6 Hz, Ar^1–*H*), 6.88 (1H, s, Ar–*H*), 5.62 (1H, d, *J* = 6.18 Hz, Ar–C*H*O–), 5.32 (2H, s, –OCH_2–), 2.65–2.69 (1H, m, –CHC*H*CH_3), 2.46–2.59 (3H, m, Ar–CH_2–, –*CH*CHCH_3), 2.30 and 2.24 (3H each, s, 2× Ar–CH_3), 1.79–1.89 and 1.67–1.77 (1H each, m, Ar–CH_2CH_2–), 1.39 (3H, d, *J* = 7.30 Hz, CH_3CH–). ^{13}C NMR (100 MHz $CDCl_3$): δ 179.54, 157.58 ($^1J_{CF}$ = 255.57 Hz), 154.38, 144.95, 141.39 ($^4J_{CF}$ = 2.01 Hz), 134.34, 131.06, 130.16 ($^3J_{CF}$ = 4.02 Hz), 129.0, 126.35, 125.74 ($^3J_{CF}$ = 17.02 Hz), 124.85, 122.44, 115.57, 80.84 ($^2J_{CF}$ = 26.16 Hz), 75.71, 63.15, 41.83, 40.50, 23.73, 23.66, 19.94, 14.52, 11.7. IR γ_{max} (neat): 3391, 2928, 1765, 1599, 1485, 1448, 1381, 1297, 1222, 1202, 1164, 1124, 1020, 986, 949, 903, 882, 856, 813, 769, 706, 667, 571 cm^{-1}. HRMS *m/z* calcd for $C_{24}H_{22}BrFIN_3O_3$ $[M + H]^+$ 625.99460, found 625.99461.

*4.1.5.17. Synthesis of 2-bromo-4,5-difluoro-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**21**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (100 mg, 0.35 mmol) and 2-bromo-4,5-difluoro phenyl boronic acid (100 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **21** (177 mg, 98% yield). Yellow solid; mp: 92–95 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (1H, s, –NC*H*–) 7.63 (1H, dd, *J* = 9.09 and 7.40 Hz, Ar^1–*H*), 7.59 (1H, dd, *J* = 9.20 and 7.44 Hz, Ar^1–*H*), 6.90 (1H, s, Ar–*H*), 5.61 (1H, d, *J* = 6.18 Hz, Ar–C*H*O–), 5.31 (2H, s, –OCH_2–), 2.66–2.70 (1H, m, –CHC*H*CH_3), 2.42–2.56 (3H, m, Ar–CH_2–, –*CH*CHCH_3), 2.29 and 2.25 (3H each, s, 2× Ar-CH_3), 1.83–1.93 and 1.69–1.79 (1H each, m, $ArCH_2CH_2$–), 1.39 (3H, d, *J* = 7.30 Hz, CH_3CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.51, 154.38, 151.23 ($^{1,2}J_{CF}$ = 256.23, 20.35 Hz), 148.56 ($^{1,2}J_{CF}$ = 253.56, 21.23 Hz), 144.92, 134.37, 132.42 ($^3J_{CF}$ = 8.21 Hz), 131.12, 128.99, 126.30, 124.58, 122.50 ($^2J_{CF}$ = 21.09 Hz), 117.64 ($^2J_{CF}$ = 21.16 Hz), 115.43, 113.43 ($^3J_{CF}$ = 7.81 Hz), 75.70, 62.95, 41.85, 40.48, 23.72, 23.66, 19.96, 14.52, 11.73. IR γ_{max} (neat): 3830, 3477, 2929, 1765, 1601, 1509, 1377, 1296, 1224, 1165, 1121, 1040, 949, 861, 800, 705, 670, 630, 566, 528 cm^{-1}. HRMS *m/z* calcd for $C_{24}H_{22}BrF_2N_3O_3$ $[M + H]^+$ 518.08853, found 518.08782.

*4.1.5.18. Synthesis of 3-chloro-4-propoxy-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**22**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (86 mg, 0.30 mmol) and 3-chloro-4-propoxyphenyl boronic acid (77 mg, 0.36 mmol) as per method described in Section 4.1.5 to give **22** (147 mg, 99% yield). Colourless solid; mp: 161–162 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (1H, s, –NC*H*–), 7.59 (1H, d, *J* = 8.54 Hz, Ar^1–*H*), 7.03 (1H, d, *J* = 8.78 Hz, Ar^1–*H*), 6.88 (1H, s, Ar–H), 5.62 (1H, d, *J* = 6.14 Hz, Ar–C*H*O–), 5.27 (2H, s, –OCH_2–), 4.05 (2H, t, *J* = 6.48 Hz, –OCH_2CH_2–), 2.59–2.63 (1H, m, –CHC*H*CH_3), 2.42–2.56 (3H, m, Ar–CH_2–, –*CH*CHCH_3), 2.31 and 2.24 (3H each, s, 2× Ar–CH_3), 1.92 (2H, m, –CH_2CH_3), 1.80–1.89 and 1.65–1.75 (1H each, m, $ArCH_2CH_2$–), 1.39 (3H, d, *J* = 7.31 Hz, CH_3CH–), 1.09 (3H, t, *J* = 7.4 Hz, –CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.58, 155.07, 154.44, 134.37, 134.11, 131.06, 129.11, 128.82, 126.13, 124.04, 122.97, 120.15, 115.10, 113.52, 75.74, 71.06, 62.8, 41.85, 40.50, 23.76, 23.71, 22.43, 19.99, 14.52, 11.75, 10.45. IR γ_{max} (neat): 3449, 2936, 1765, 1595, 1508, 1382, 1292, 1166, 1122, 1051, 981, 950, 856, 807, 673, 585, 540 cm^{-1}. HRMS *m/z* calcd for $C_{27}H_{30}ClN_3O_4$ $[M + H]^+$ 496.19976, found 496.19907.

*4.1.5.19. Synthesis of 3-bromo-2-methoxy-5-methyl-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**23**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (71 mg, 0.25 mmol) and 3-bromo-2-methoxy-5-methyl phenyl boronic acid (73 mg, 0.30 mmol) as per method described in Section 4.1.5 to give **23** (127 mg, 97% yield). Yellow solid; mp: 123–125 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21 (1H, s, −NC*H*−), 7.58 (1H, d, J = 1.2 Hz, Ar^1−*H*), 7.51 (1H, d, J = 1.6 Hz, Ar^1−*H*), 6.92 (1H, s, Ar−*H*), 5.64 (1H, d, J = 6.15 Hz, Ar−C*H*O−), 5.32 (2H, s, −OC*H*$_2$−), 3.56 (3H, s, −OC*H*$_3$), 2.64–2.68 (1H, m, −CHC*H*CH$_3$), 2.45–2.59 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.41 (3H, s, Ar−C*H*$_3$), 2.31 and 2.26 (3H each, s, 2× Ar−C*H*$_3$), 1.80–1.90 and 1.65–1.74 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.41 (3H, d, J = 7.4 Hz, C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.49, 154.43, 147.08, 144.92, 136.36, 134.43, 134.24, 131.34, 131.04, 128.79, 126.23, 125.34, 124.20, 117.98, 115.22, 75.69, 62.87, 61.16, 41.81, 40.49, 23.71, 23.66, 20.55, 19.95, 14.50, 11.69. IR γ_{max} (neat): 2926, 1767, 1597, 1482, 1378, 1297, 1225, 1166, 1120, 1041, 988, 949, 856, 783, 766, 702, 568 cm^{-1}. HRMS m/z calcd for $C_{26}H_{28}BrN_3O_4$ [M + H]$^+$ 526.13359, found 526.1333.

*4.1.5.20. Synthesis of 2-bromo-6-fluoro-3-methoxy-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**24**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (115 mg, 0.40 mmol) and 2-bromo-6-fluoro-3-methoxy phenyl boronic acid (120 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **24** (207 mg, 98% yield). Colourless solid; mp: 159–165 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81 (1H, s, −NC*H*−), 7.22–7.30 (1H, m, Ar^1−*H*), 7.04–7.10 (1H, m, Ar^1−*H*), 6.89 (1H, s, Ar−*H*), 5.62 (1H, d, J = 6.15 Hz, Ar−C*H*O−), 5.32 (2H, s, −O−C*H*$_2$−), 3.95 (3H, s, −OC*H*$_3$), 2.66–2.70 (1H, m, −CHC*H*CH$_3$), 2.45–2.59 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.30 and 2.24 (3H each, s, 2× Ar−C*H*$_3$), 1.81–1.91 and 1.64–1.74 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.39 (3H, d, J = 7.22 Hz, C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.63, 154.44, 153.40 ($^2J_{CF}$ = 2.12 Hz), 152.0 ($^1J_{CF}$ = 248.34 Hz), 145.27, 134.33, 131.00, 128.96, 126.32, 125.27, 115.29, 115.62, 115.40 ($^2J_{CF}$ = 26.0 Hz), 113.86 ($^3J_{CF}$ = 8.23 Hz), 112.22, 75.76, 63.18, 57.17, 41.82, 40.54, 23.73, 23.67, 19.93, 14.50, 11.70. IR γ_{max} (neat): 3476, 2920, 1763, 1598, 1457, 1298, 1039, 947, 852, 808, 750, 699, 642, 542, 503 cm^{-1}. HRMS m/z calcd for $C_{25}H_{25}BrFN_3O_3$ [M + H]$^+$ 530.108524, found 530.1078.

*4.1.5.21. Synthesis of 2-trifluoromethyl-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**25**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (65 mg, 0.23 mmol) and 2-(trifluoromethyl) phenyl boronic acid (52 mg, 0.28 mmol) as per method described in Section 4.1.5 to give **25** (105 mg, 97% yield). Colourless solid; mp: 148–150 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87–1.90 (2H, m, −NC*H*− and Ar^1−H), 7.80–7.60 (2H, m, Ar^1−*H*), 7.59 (1H, d, J = 8.16 Hz, Ar^1−*H*), 6.89 (1H, s, Ar−*H*), 5.62 (1H, d, J = 6.18 Hz, Ar−C*H*O−), 5.32 (2H, s, −OC*H*$_2$−), 2.62–2.66 (1H, m, −CHC*H*CH$_3$), 2.45–2.58 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.29 and 2.24 (3H each, s, 2× Ar−C*H*$_3$), 1.83–1.93 and 1.63–1.74 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.39 (3H, d, J = 7.30 Hz, −C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.57, 154.45, 144.78, 134.82 ($^2J_{CF}$ = 46.0 Hz), 134.36, 133.12, 131.04, 130.51, 129.07, 128.92, 127.36 ($^3J_{CF}$ = 4.16 Hz), 126.71, 126.32 ($^3J_{CF}$ = 3.2 Hz), 125.25 ($^4J_{CF}$ = 1.60 Hz), 122.63 ($^1J_{CF}$ = 272.0 Hz), 115.49, 75.74, 63.03, 41.85, 40.50, 23.72, 23.66, 19.91 14.51, 11.66. IR γ_{max} (neat): 3436, 2927, 1766, 1600, 1460, 1314, 1127, 1041, 856, 787, 710, 666, 637, 564, 457 cm^{-1}. HRMS m/z calcd for $C_{25}H_{24}F_3N_3O_3$ [M + H]$^+$ 472.18425, found 472.18426.

*4.1.5.22. Synthesis of 4-bromo-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-naphthalene (**26**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (101 mg, 0.35 mmol) and 4-bromonaphthalen-1-yl-1-boronic acid (106 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **26** (182 mg, 98% yield). Yellow gummy mass. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.37 (1H, d, J = 8.17 Hz, Ar^1−*H*), 8.01 (1H, s, =NC*H*−), 7.92 (1H, d, J = 7.96 Hz, Ar^1−*H*), 7.75–7.62 (3H, m, Ar^1−*H*), 7.49 (1H, d, J = 7.90 Hz, Ar^1−*H*), 6.96 (1H, s, Ar−*H*), 5.62 (1H, d, J = 6.16, Ar−C*H*O−), 5.34 (2H, s, −OC*H*$_2$−), 2.66–2.70 (1H, m, −CHC*H*CH$_3$), 2.41–2.55 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.31 and 2.27 (3H each, s, 2× Ar−C*H*$_3$), 1.79–1.89 and 1.61–1.72 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.39 (3H, d, J = 7.32, C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.54, 154.48, 134.39, 133.5, 132.59, 131.10, 130.90, 129.65, 129.08, 128.97, 128.84, 128.76, 128.55, 127.83, 126.28, 125.33, 123.94, 122.88, 115.41, 75.71, 63.11, 41.83, 40.50, 23.73, 23.66, 19.98, 14.51, 11.74. IR γ_{max} (neat): 3838, 2919, 1759, 1461, 1375, 1166, 1036, 933, 895, 809, 633, 555, 525 cm^{-1}. HRMS m/z calcd for $C_{28}H_{26}BrN_3O_3$ [M + H]$^+$ 532.12303, found 532.12173.

*4.1.5.23. Synthesis of 2-(3-bromo benzyloxy)-3-bromo-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**27**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (114 mg, 0.40 mmol) and 2-{(3-bromophenoxy) methyl}-3-bromo phenyl boronic acid (185 mg, 0.48 mmol) as per method described in Section 4.1.5 to give **27** (263 mg, 99% yield). Yellow solid mp: 147–148.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (1H, s, −NC*H*−), 7.73 (2H, dd, J = 8.10 and 1.42 Hz, Ar^1−*H*), 7.37–7.44 (2H, m, Ar^1−*H*), 7.22 (1H, d, J = 8.18 Hz, Ar^1−*H*), 7.06–7.16 (2H, m, Ar^1−*H*), 6.90 (1H, s, Ar−*H*), 5.60 (1H, d, J = 6.14 Hz, Ar−C*H*O−), 5.25 (2H, s, −OC*H*$_2$−), 4.69 (2H, s, Ar−C*H*$_2$O−), 2.62–2.66 (1H, m, −CHC*H*CH$_3$), 2.41–2.55 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.24 (6H, s, 2× Ar−C*H*$_3$), 1.81–1.92 and 1.65–1.76 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.39 (3H, d, J = 7.32 Hz, C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.53, 154.50, 148.19, 144.93, 137.32, 134.42, 134.28, 132.53, 131.80, 131.57, 131.04, 130.13, 128.79, 127.06, 126.35, 126.23, 125.37, 124.58, 122.50, 118.81, 115.11, 75.70, 75.17, 62.85, 41.85, 40.50, 23.72, 23.67, 19.97, 14.52, 11.71. IR γ_{max} (neat): 2926, 1767, 1574, 1481, 1375, 1296, 1229, 1166, 1121, 1039, 950, 862, 787, 696, 662, 465 cm^{-1}. HRMS m/z calcd for $C_{31}H_{29}Br_2N_3O_4$ [M + H]$^+$ 666.05975, found 666.05857.

*4.1.5.24. Synthesis of 2-chloro-5-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-pyridine (**28**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (129 mg, 0.45 mmol) and 6-chloro pyridine-3-yl-3-boronic acid (89 mg, 0.54 mmol) as per method described in Section 4.1.5 to give **28** (191 mg, 97% yield). Yellow solid; mp: 161–163 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.81 (1H, d, J = 1.89 Hz, Ar^1−*H*), 8.14 (1H, dd, J = 8.68 and 2.72 Hz, Ar^1−*H*), 8.09 (1H, s, −NC*H*−), 7.52 (1H, d, J = 8.55 Hz, Ar^1−*H*), 6.88 (1H, s, Ar−*H*), 5.61 (1H, d, J = 6.17 Hz, Ar−C*H*O−), 5.29 (2H, s, −OC*H*$_2$−), 2.66–2.70 (1H, m, −CHC*H*CH$_3$), 2.41–2.56 (3H, m, Ar−C*H*$_2$−, −C*H*CHCH$_3$), 2.29 and 2.24 (3H each, s, 2× Ar−C*H*$_3$), 1.80–1.90 and 1.65–1.76 (1H each, m, Ar−CH$_2$C*H*$_2$−), 1.38 (3H, d, J = 7.28 Hz, C*H*$_3$CH−). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.64, 154.27, 151.16, 146.23, 141.16, 134.39, 132.69, 131.05, 130.79, 128.98, 126.01, 125.17, 122.73, 115.01, 75.72, 62.64, 41.75, 40.49, 23.68, 23.62, 19.95, 14.49, 11.67. IR γ_{max} (neat): 3456, 2926, 1765, 1481, 1300, 949, 748, 692, 586, 548, 512 cm^{-1}. HRMS m/z calcd for $C_{23}H_{23}ClN_4O_3$ [M + H]$^+$ 439.15314, found 439.15253.

*4.1.5.25. Synthesis of 4-formyl-1-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzene (**29**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (71 mg, 0.25 mmol) and 4-formyl phenyl boronic acid (45 mg, 0.30 mmol) as per method described in Section 4.1.5 to give **29** (105 mg, 98% yield). Yellow solid; mp: 212–217 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.08 (1H, s, −C*H*O), 8.15 (1H, s, −NC*H*−), 8.07 (2H, d, J = 8.61 Hz,

Ar^1–*H*), 7.98 (2H, d, *J* = 8.67 Hz, Ar^1–*H*), 6.89 (1H, s, Ar–*H*), 5.62 (1H, d, *J* = 6.13 Hz, Ar–C*H*O–), 5.31 (2H, s, –OCH_2–), 2.63–2.67 (1H, m, –CHC*H*CH_3), 2.45–2.59 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.31 and 2.24 (3H each, s, 2× Ar–CH_3), 1.81–1.91 and 1.60–1.69 (1H each, m, Ar–CH_2CH_2–), 1.39 (3H, d, *J* = 7.27 Hz, CH_3CH–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.64, 179.57, 154.34, 146.11, 140.91, 136.06, 134.41, 131.34 (2CH), 130.91, 128.94, 128.83, 126.08, 120.56 (2CH), 115.03, 75.71, 62.79, 41.80, 40.47, 23.69, 23.63, 19.97, 14.51, 11.74. IR γ_{max} (neat): 3480, 2932, 1764, 1700, 1601, 1478, 1298, 1208, 1167, 1124, 987, 949, 838, 733, 672, 571, 527 cm^{-1}. HRMS *m*/*z* calcd for $C_{25}H_{25}N_3O_4$ $[M + H]^+$ 432.19178, found 432.19179.

*4.1.5.26. Synthesis of 3-{(5-α-desmotroposantonin)methyl-1H-1,2,3-triazolyl}-benzamide (**30**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (85 mg, 0.30 mmol) and 3-carbamoyl phenyl boronic acid (60 mg, 0.36 mmol) as per method described in Section 4.1.5 to give **30** (131 mg, 98% yield). Colourless solid; mp: 210 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.40 (1H, s, Ar^1–*H*), 8.19 (1H, s, –*NCH*–), 8.09 (1H, dd, *J* = 8.04 and 1.16 Hz, Ar^1–*H*), 7.99 (1H, d, *J* = 7.95 Hz, Ar^1–*H*), 7.72 (1H, dd, *J* = 8.12 and 7.92 Hz, Ar^1–H), 7.12 (1H, s, Ar–*H*), 5.70 (1H, d, *J* = 6.01 Hz, Ar–C*H*O–), 5.23 (2H, s, –OCH_2–), 2.65–2.69 (1H, m, –CHC*H*CH_3), 2.44–2.58 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.23 and 2.19 (3H each, s, 2× Ar–CH_3), 1.81–1.91 and 1.45–1.59 (1H each, m, ArCH_2CH_2–), 1.27 (3H, d, *J* = 7.4 Hz, CH_3CH–). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.60, 167.20, 154.44, 145.05, 137.04, 136.44, 134.44, 131.52, 130.45, 129.31, 128.06, 125.30, 123.25, 123.09, 119.66, 115.54, 75.61, 62.41, 41.18, 40.41, 23.65, 23.54, 19.99, 14.60, 11.93. IR γ_{max} (neat): 3732, 3314, 2918, 1764, 1681, 15,852, 1461, 1299, 1170, 1126, 1050, 994, 944, 899, 845, 775, 720, 654 cm^{-1}. HRMS *m*/*z* calcd for $C_{25}H_{26}N_4O_4$ $[M + H]^+$ 447.20268, found 447.20242.

*4.1.5.27. Synthesis of 1-N-acetyl-4-{(4-(5-α-desmotroposantonin) methyl-1H-1,2,3-triazolyl}phenyl)-aniline (**31**).* The title compound prepared by the reaction of propargylated α-desmotroposantonin (99.5 mg, 0.35 mmol) and 4-carbamoyl phenyl boronic acid (75 mg, 0.42 mmol) as per method described in Section 4.1.5 to give **31** (159 mg, 99% yield). Yellow solid; mp: 175–179 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92–7.98 (2H, m, Ar^1–*H* and –NC*H*–), 7.84 (1H, d, *J* = 6.54 Hz, Ar^1–*H*), 7.36–7.43 (2H, m, Ar^1–*H*), 6.90 (1H, s, Ar–*H*), 5.63 (1H, d, *J* = 6.14 Hz, Ar–C*H*O–), 5.26 (2H, s, –OCH_2–), 2.62–2.66 (1H, m, –CHC*H*CH_3), 2.46–2.58 (3H, m, Ar–CH_2–, –C*H*CHCH_3), 2.21 (9H, s, 2× Ar–CH_3 and –NCOCH_3), 1.83–1.93 and 1.64–1.71 (1H each, m, Ar–CH_2CH_2–), 1.39 (3H, d, *J* = 7.24 Hz, CH_3CH–). ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.10, 169.24, 154.27, 145.01, 139.83, 137.12, 134.52, 130.87, 130.23 (2CH), 129.14, 126.50, 120.02, 116.06, 115.85, 111.70, 76.03, 63.23, 41.62, 40.45, 24.42, 23.54, 23.48, 19.91, 14.43, 11.70. IR γ_{max} (neat): 3477, 2922, 1770, 1472, 1346, 1049, 778, 688, 644, 558, 548, 490 cm^{-1}. HRMS *m*/*z* calcd for $C_{26}H_{28}N_4O_4$ $[M + H]^+$ 461.21833, found 461.21749.

4.2. Biology

Mitogens and reagents: Concanavalin A (ConA), lipopolysaccharide (LPS, *Escherichia coli* 055:B5), 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT), and 3,3′,5,5′-tetramethylbenzidine (TMB) were procured from Sigma Aldrich. RPMI (Roswell Park Memorial Institute) 1640 medium was purchased from Gibco BRL, Life Technologies (USA). Fetal bovine serum (FBS) was purchased from HyClone Laboratories (Utah, USA). *Animals*. Balb/c mice 10–12 week old and weighing 20–24 g obtained from animal house of Indian Institute of Integrative Medicine, Jammu were taken up in groups of six and employed for the study. These animals were maintained at a room temperature of 26 ± 2 °C with 12 h light/dark cycle with free access to pellet food and water. All husbandry and experimental contact made with the mice maintained specific pathogen-free conditions. Animals used in experimental work received humane care as per the ethical regulations on animal research. Animals were housed and maintained following standard guidance as found in Government of India guidelines [38]. The study protocol was approved by Institutional Animal Ethics Committee.

4.2.1. Determination of cytotoxic effect of different samples by MTT assay (in vitro)

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, first described by Mosmann in 1983, is based on the ability of a mitochondrial dehydrogenase enzyme from viable cells to cleave the tetrazolium rings of the pale yellow MTT and form a dark blue formazan crystals which is largely impermeable to cell membranes, thus resulting in its accumulation within healthy cells. Solubilization of the cells by the addition of a detergent results in the liberation of the crystals which are solubilized [39–41]. The number of surviving cells is directly proportional to the level of the formazan product created. The colour can then be quantified using a simple colorimetric assay [42,43]. The results can be read on a multiwell scanning spectrophotometer (ELISA reader) in the wavelengths of 450, 540 and 620 nm respectively.

Methodology: Animals (Balb/c mice, 18–22 g) were sacrificed; their spleens were removed in sterile conditions. A single cell suspension was prepared in 5 mL of incomplete RPMI. The cell suspension was centrifuged at 1200 rpm for 10 min and supernatant was discarded. RBCs were lysed by Tris-ammonium chloride treatment. The cells were centrifuged twice at 1200 rpm for 10 min, supernatant discarded and resuspended in complete RPMI. The viability of cells was checked with trypan blue. 1×10^6 cells/mL suspension was prepared and 100 μL of it was poured in each well of 96 well microtitre plate (Flat bottom). An aliquot of 50 μL of standard mitogens (ConA = 10 μg/mL and LPS = 10 μg/mL) and test materials were added according to the experimental setup. 50 μL of drug of interest of different concentrations (1, 10 and 100 μM) (**1**–**31**) was dissolved in DMSO and added to each well of flat bottom microtitre 96 well plate. Plates were placed on a shaker for 5 min to thoroughly mix the samples into the media.

The plates were incubated for 48 h in CO_2 incubator (37 °C, 5% CO_2 and 90% relative humidity). After 48 h incubation, plates were taken out from the CO_2 incubator. 10 μL of MTT solution (5 mg/mL in PBS) was added to each well (MTT in solution is not stable for long-term). The contents were placed on a shaker for 5 min to thoroughly mix the MTT into the media. Plates were incubated for 4–6 h in CO_2 incubator (37 °C, 5% CO_2 and 90% relative humidity) to allow the MTT to be metabolized. Centrifuged the plates at 2000 rpm for 10 min. Removed the medium (dry plate on paper towels to remove residue if necessary). Resuspended formazan crystals (MTT metabolic product) in 100 μL of DMSO. Mechanically mixed the plate until formazan crystals were dissolved. Read in a microculture plate reader at test and reference wavelengths of 450, 540 and 620 nm respectively. The mean of the optical density of plates were calculated and evaluate the percentage of each value verses control.

Acknowledgements

The authors are thankful Taxonomists of institute (Dr SN Sharma and S. Kitchalu) for providing the authentic plant material. Authors (PKC, SF and RRA) thank Council of Scientific and Industrial Research (CSIR-UGC), New Delhi for the award of senior research fellowships. Staff of instrumentation division (NMR) of

our institute is well acknowledged for recording the spectroscopic data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2012.12.018.

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