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Short communication

1,2,3-Triazole tethered β-lactam-Chalcone bifunctional hybrids: Synthesis and anticancer evaluation

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ABSTRACT

The manuscript describes the synthesis of novel 1,2,3-triazole tethered β-lactam-chalcone bifunctional hybrids *via* click chemistry approach utilizing azide-alkyne cycloaddition reactions and their evaluation as anticancer agents against four human cancer cell lines. The presence of a cyclohexyl substituent at N-1 of β-lactam ring and methoxy substituents, preferably *ortho* on ring A and *para* on ring B on chalcones markedly improved the anticancer profiles of the synthesized scaffolds with the most potent of the test compound exhibiting an IC_{50} value of <1, 67.1, <1 and 6.37 μM against A-549(lung), PC-3(prostate), THP-1(leukemia), and Caco-2(colon) cell lines, respectively.

1. Introduction

Cancer, the uncontrolled, rapid and pathological proliferation of abnormal cells, is one of the most formidable afflictions in the world [1,2]. Despite immense advances in the field of basic and clinical research, which have resulted in higher cure rates for a number of malignancies, cancer remains the second leading cause of death after heart disorders in developing as well as advanced countries. Many of the currently available anticancer drugs are unable to differentiate between normal and neoplastic cells or to overcome primary or secondary resistance mechanisms evolved in the cancer cells. Thus, there is a pressing need for new anticancer agents with high potency, less toxicity in non-cancerous cells, and unique targets of action [3]. Currently, cancer therapy interfering with a single biological molecule or pathway has been successfully utilized [4]. However, there is general belief that agents modulating more than one target could have superior efficacy compared to single target drugs [5,6]. Therefore, modulating multiple targets simultaneously can be achieved by the combination of multiple drugs with different mechanisms or by single chemical entity that could modulate several targets of a multi-factorial disease. As a result, there is increasing interest in the discovery of agents that concomitantly address more than one biological target for cancer treatment [7,8].

Molecular hybridization is the rational design of new chemical entities by the fusion of two drugs, both active compounds and/or pharmacophoric units recognized and derived from known bioactive molecules [9,10]. Pharmacophore hybridization is believed to be analogous to conventional combination therapy, with the exception that the two drugs are covalently linked and available as a single entity [11]. The selection of the two principles in the dual drug is usually based on their observed (or anticipated) synergistic or additive pharmacological activities to enable the identification of highly active novel chemical entities. Chalcones (1,3-diaryl-2-propen-1-ones) constitute an important class of natural products belonging to the flavonoids family, display interesting biological activities [12–17]. The appeal of working with chalcones stems from their synthetic accessibility, the various ways the core structure can be diversified and their ability to confer drug-like properties to compound libraries modelled on them [18]. Chalcones received significant attention for their anti-tumor properties, particularly in view of their similar mode of action to the

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structurally related natural combretastatin [19]. Recent studies have shown that triazole based chalcone-pyrrolo[2,1-c] [1,4] benzodiazepine (PBD) hybrids resulted in G1 cell cycle arrest and exhibited inhibitory effect on NF-kB, Bcl-XL proteins which are vital for breast cancer cell proliferation [20]. Chalcone is also considered to be a promising template to develop inhibitors of HIF-1 [21], a major mechanism for the survival and evasion of tumor cells.

Triazoles constitute another important class of heterocycles because of their varied biological activities [22] and being regarded as an interesting unit with significant anticancer profile in many of the human cell lines [23–25]. The triazoles are more than just passive linkers, and confer properties like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions [26].

β-Lactam compounds are 'evergreen' bioactive molecules with activity ranging from the antimicrobial potency of naturally occurring bicyclic compounds (penicillins and cephalosporins), to the new variants with monocyclic structure (azetidinones) having specific biological activities. Since, β-lactams are widely and safely used without significant toxicity, synthesis and utilization of these molecules as new, novel anticancer agents could be timely and significant. Recent relevant studies on β-lactams have shown their potential as anti-tumor agents against a number of human tumor and normal cell lines [27]. The 1,4-diaryl-2-azetidinones specifically, have shown anti-proliferative activity against the MCF-7 and MDA-MB-231 human breast carcinoma cell lines exerting antimitotic effects through inhibition of tubulin polymerisation and subsequent G2/M arrest of the cell cycle [28].

Recent revelation from our lab has shown triazole tethered 2-azetidinones as potential anticancer agent against different human cancer cell lines with marked dependency of activity on the substituents at N-1 of the β-lactam ring and C-3 substituted triazole ring [29]. In continuation of our pursuit towards the synthesis of biologically potent novel functional entities [30], we report herein the synthesis of 1,2,3-triazole tethered novel bifunctional hybrids of β-lactams with functionalized chalcones *via* azide-alkyne cycloaddition reaction (Fig. 1) and their evaluation as anticancer agents against four human cancer cell lines *viz.* A-549(lung), PC-3(prostate), THP-1(leukemia), and Caco-2(colon).

2. Synthetic chemistry and pharmacology

2.1. Synthetic chemistry

The acetylenic chalcones (**1a–c, 2a–b** and **3**) required for the synthesis of desired target compounds were prepared according to reported procedures [31] while 3-azido-2-azetidinones (**4** and **5**) were synthesized by Staudinger reaction of appropriately functionalized 1-azadienes with azido-ketene[29]. The target compounds (**6–11**) were synthesized by utilizing azide-alkyne cycloaddition reaction of appropriate precursors in the presence of $CuSO_4.5H_2O$/sodium ascorbate in ethanol: water mixture. The methodology involved the initial stirring of an equimolar mixture of acetylenic chalcones (**1a–c** or **2a–b**) or acetylenic vanillin **3** with 3-azido-2-azetidinones (**4, 5**) in ethanol: water mixture with subsequent addition of $CuSO_4 \cdot 5H_2O$ (0.05 mmol) and sodium ascorbate (0.13 mmol) (Schemes 1 and 2). The reaction mixture was stirred at room temperature for 7–8 h and the progress was monitored using tlc. The purification of the reaction mixture, after usual work up, *via* column chromatography resulted in the isolation of desired scaffolds, the structures to which are assigned on the basis of spectral data and analytical evidences.

2.2. Pharmacology

The human cancer cell lines were procured from National Cancer Institute, Frederick, PO Box B, Frederick, MD 21702-1201, U.S.A. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4, supplemented with 10% fetal calf serum, 100 μg/ml streptomycin and

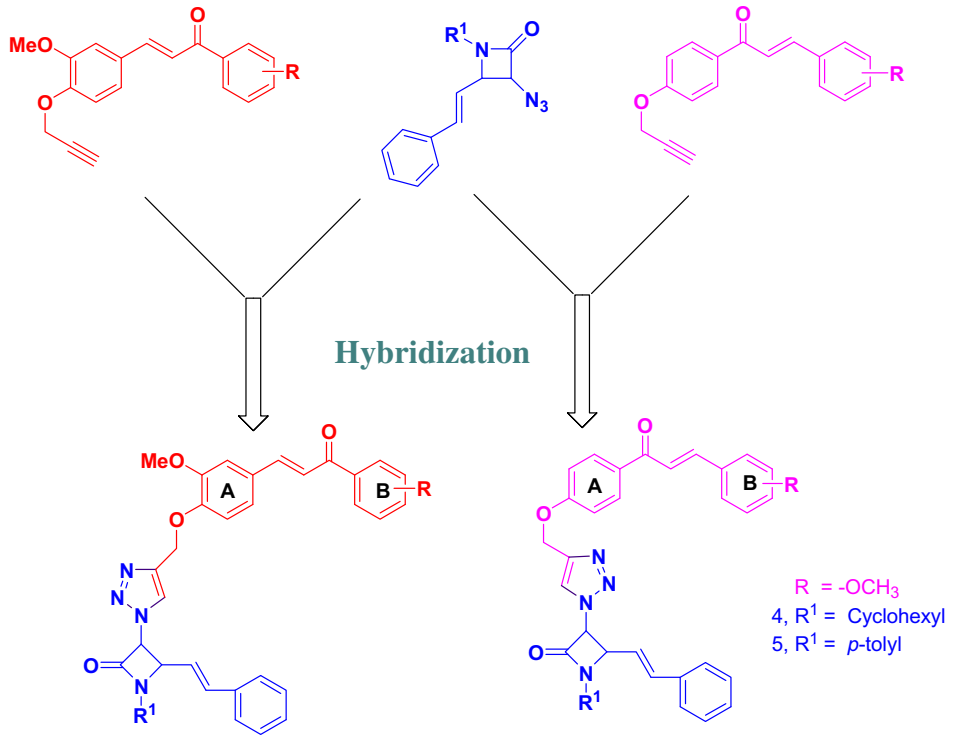
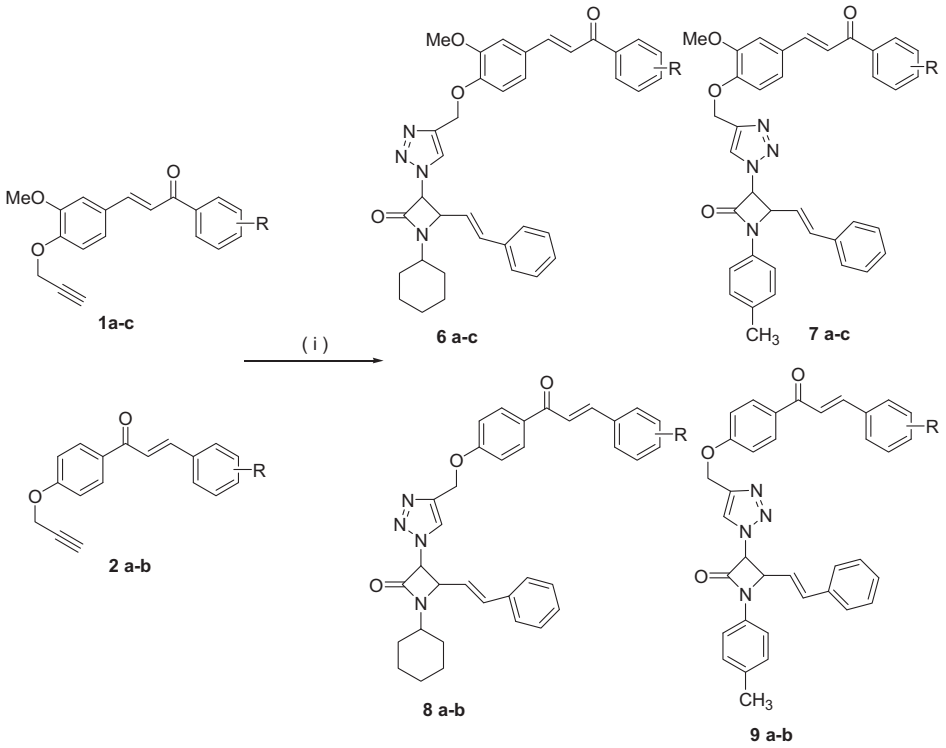


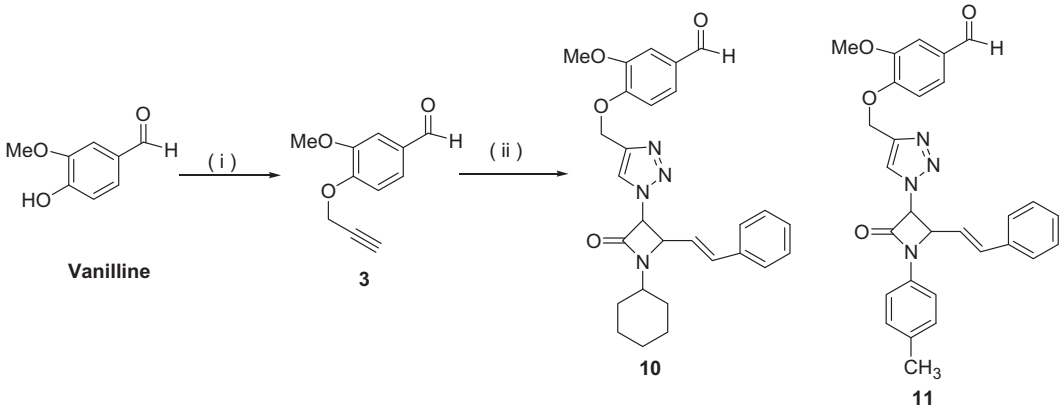
Fig. 1. General structure of lead compound and target hybrid compounds



Scheme 1. Reagent and conditions: (i) **4** (for **6a**–**c** and **8a**–**b**) or **5** (for **7a**–**c** and **9a**–**b**), Sodium ascorbate (0.13 mmol), $CuSO_4 \cdot 5H_2O$ (0.05 mmol), EtOH/H_2O, rt, 8 h.

100 units/ml penicillin) in a carbon dioxide incubator (37 °C, 5% CO_2, 90% RH). The cells at subconfluent stage were harvested from the flask by treatment with trypsin [0.05% in PBS (pH 7.4) containing 0.02% EDTA]. Cells with viability of more than 98% as determined by trypan blue exclusion, were used for determination of cytotoxicity. The cell suspension of 1×10^5 cells/ml was prepared in complete growth medium. Stock solutions (2×10^{-2} M) of compounds were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μg/ml of gentamycin to obtain working test solutions of required concentrations.

In vitro cytotoxicity against human cancer cell lines of different tissues was determined [32,33] using 96-well tissue culture plates. The 100 μl of cell suspension was added to each well of the 96-well tissue culture plate. The cells were allowed to grow in carbon dioxide incubator (37 °C, 5% CO_2, 90% RH) for 24 h. Test materials in complete growth medium (100 μl) were added after 24 h of incubation to the wells containing cell suspension. The plates were further incubated for 48 h in a carbon dioxide incubator. The cell growth was stopped by gently layering trichloroacetic acid (50%, 50 μl) on top of the medium in all the wells. The plates were incubated at 4 °C for 1 h to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove trichloroacetic acid, growth medium low molecular weight metabolites, serum proteins, etc. and air-dried. The plates were stained with Sulforhodamine B dye (0.4% in 1% acetic acid, 100 μl) for 30 min. The plates were washed five times with 1% acetic acid and then air-dried [33]. The adsorbed dye was dissolved in Tris–HCl Buffer (100 μl, 0.01 M, pH 10.4) and plates were gently stirred for 10 min on a mechanical stirrer. The optical density (OD) was recorded on ELISA reader at 540 nm. The cell growth was



Scheme 2. Reagent and conditions: (i) K_2CO_3, DMF, propargyl bromide, rt, 12 h (ii) **4** (for **10**) or **5** (for **11**), sodium ascorbate (0.13 mmol), $CuSO_4 \cdot 5H_2O$ (0.05 mmol), EtOH/H_2O, rt, 8 h.

determined by subtracting mean OD value of respective blank from the mean OD value of experimental set. Percent growth in presence of test material was calculated considering the growth in absence of any test material as 100% and in turn percent growth inhibition in presence of test material was calculated.

3. Result and discussions

The synthesized β-lactam-chalcone hybrids were evaluated for their anticancer activity against four human cancer cell lines *viz.* A-549(lung), PC-3 (prostate), THP-1(leukemia) and Caco-2 (colon) using sulforhodamine B assay. The concentration dependent cytotoxicity of these scaffolds against human cancer cell lines is shown in Table 1. Paclitexal has been used as standard in case of lung (A-549), 5-fluorouracil in case of THP-1(leukemia) and Caco-2(colon) while mitomycin in case of PC-3(prostate). As evident from Table 1, the tested compounds were not as active as paclitexal and mitomycin C in terms of %age growth inhibition against A-549 and PC-3 cell lines. However, the compound **6a** has shown twice the **%** growth inhibition than 5-fluorouracil in case of THP-1 cell line and comparable growth inhibition with 5-fluorouracil against Caco-2 cell lines. The careful analysis of Table 1 reveals interesting structure activity relationship (SAR) and substituent effect with considerable % growth inhibition at 10 μM. The compounds with cyclohexyl substituent **(6a–6c)** on *N*–1 of β-lactam ring have shown better cytotoxic activity compared to *N*-aryl-β-lactams **(7a–7c)** against all the cell lines tested. The trend reverses on comparing **8a–b** and **9a–b** where *N*-aryl substituted bifunctional hybrids showed better growth inhibition than their cyclohexyl counterparts. Further, vanillin based chalcones (**6a–c** and **7a–c**) showed better growth inhibition compared to **8a–b** and **9a–b** which might be either because of the presence of an ortho-methoxy substituent on ring A.

The presence of methoxy substituent and its position on ring B has shown to play an important role on the observed growth inhibition. Evidently, a single methoxy group on ring B, preferably at the *para*-position considerably improves the activity profile (compare **6a** and **6b**) while a decrease in activity has been observed especially in case of PC-3 and THP-1 cell lines when un-substituted phenyl ring B was employed (**6c**). The favourable effect of 4-methoxy on activity profiles is further authenticated on comparing **7a** and **7b** especially in case of Caco-2 cell lines. As illustrated in Table 1, the introduction of an additional methoxy group at *ortho* position in case of **7b** resulted in the decrease in activity in case of Caco-2 cell lines. However the compound **7c** (un-substituted ring B) shows an exception and was found to be more potent than **7a** and **7b** in case of A-549 cell line and was also more potent than **7a** and **7b** in case of Caco-2 cell line especially at higher concentrations. A comparison between activity profiles of **10** and **11** (vanillin tethered β-lactams) revealed that compound **10** with *N*-cyclohexyl substituent was more

Table 1
In vitro cytotoxicity against human cancer cell lines.

Compound	R	Concentration	Tissues					
			A549	PC-3	THP-1	Caco-2	C log P	PSA (Å^2)
			%age growth inhibition					
6a	4-OCH_3	10	89	10	76	54	6.72	95.78
		50	93	33	78	57		
		100	95	79	83	72		
6b	2,4-OCH_3	10	68	29	61	16	6.81	105.01
		50	78	40	71	49		
		100	85	43	77	99		
6c	H	10	39	0	5	27	6.80	86.55
		50	67	1	11	36		
		100	82	15	28	61		
7a	4-OCH_3	10	0	1	3	26	7.27	95.78
		50	10	17	6	28		
		100	11	23	11	47		
7b	2,4-OCH_3	10	4	10	11	0	7.36	105.01
		50	15	18	14	0		
		100	23	18	25	0		
7c	H	10	26	15	0	4	7.35	86.55
		50	74	21	1	27		
		100	83	26	20	77		
8a	4-OCH_3	10	15	0	0	18	7.04	86.55
		50	49	0	0	46		
		100	80	22	10	55		
8b	2-OCH_3	10	0	17	8	0	7.04	86.55
		50	0	28	11	0		
		100	0	37	22	10		
9a	4-OCH_3	10	11	8	2	9	7.59	86.55
		50	73	8	4	44		
		100	93	9	6	98		
9b	2-OCH_3	10	43	8	0	10	7.59	86.55
		50	50	10	0	25		
		100	84	14	3	47		
10		10	39	7	10	33	4.73	86.55
		50	62	19	12	38		
		100	64	39	25	65		
11		10	45	12	0	7	5.28	86.55
		50	53	38	22	32		
		100	61	54	53	42		
Paclitaxel		1	69	–	–	–		
5-Flourouracil		20	–	–	70	68		
Mitomycin-C		1	–	60	–	–		

potent than **11** in case of Caco-2 cell lines while compound **11** with *N*-aryl substituent was observed to be more potent than **10** in case of PC-3 and THP-1 cell lines.

The IC_{50} values, which is the concentration required to inhibit 50% of cell viability by the test compounds after exposure to cells, of the test compounds against the human cell lines were calculated and the results are summarized in Table 2. Most of the compounds have show activity on A-549 and Caco-2 cell lines except **7a**, **7b** and **8b**. The tested compounds proved to be inactive against PC-3 and THP-1 cell lines except **6a** and **6b**. The vanillin based bifunctional hybrid **6a** with *N*-cyclohexyl substituent showed best IC_{50} value among the tested compounds with values of <1, 67.1, <1 and 6.37 μM against A-549, PC-3, THP-1 and Caco-2 cell lines. The compound **6b** showed a poor activity compared to **6a** except in case of A-549 cell lines where it has the comparable activity profile with **6a**. The further decrease in activity observed in case of **6c** is indicative of the role of methoxy substituent on the desired cytotoxicity.

Thus, the present communication describes the synthesis of a range of triazole tethered bifunctional hybrids of β-lactam with chalcones and their evaluation against a panel of four human cancer cell lines. The preliminary studies show that most of these compounds are active against A-549 and Caco-2 cell lines but only two of the tested compounds *viz.* **6a** and **6b** showed cytotoxic activity against PC-3 and THP-1 cell lines. The compound **6a** proved to be nearly twice as active as 5-flourouracil in case of THP-1 cell lines. These preliminary results indicate a marked dependence of cytotoxicity on the presence of cyclohexyl/aryl substituent on *N*-1 of the β-lactam and 4-methoxy substituent on ring B of the chalcone. Further, vanillin based chalcones showed better activity profiles compared to other analogues suggestive of the importance of 2-methoxy on ring A in improving cytotoxic profiles. Based on these observations, the compound **6a** may be considered as a good hit in terms of %age growth inhibition, IC_{50}, C log *P* (6.72) and PSA (95.78 $Å^2$) [34] values. Further studies in order to generalize, substantiate and improve the activity profiles of the scaffolds are underway in the lab and will soon be communicated.

4. Experimental section

Melting points were determined by open capillary using Veego Precision Digital Melting Point apparatus (MP-D) and are uncorrected. IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. ^{1}H NMR spectra were recorded in deuterochloroform with Jeol 300 (300 MHz) spectrometers using TMS as internal standard. Chemical shift values are expressed as parts per million downfield from TMS and *J* values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on Jeol 300 (75 MHz) spectrometers in deuterochloroform using TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Column chromatography was performed on a silica gel (60–120 mesh). All the starting materials as well as the products were racemates.

Table 2
IC_{50} determination of cytotoxicity of compounds against human cancer cell lines

Compound	R	Tissues			
		Lung	Prostate	Leukemia	Colon
		A-549	PC-3	THP-1	Caco-2
		IC50 (μM)			
6a	4-OCH_3	<1	67.1	<1	6.37
6b	2,4-OCH_3	<1	>100	1.39	45.2
6c	H	21.2	>100	>100	79.5
7a	4-OCH_3	>100	>100	>100	>100
7b	2,4-OCH_3	>100	>100	>100	>100
7c	H	31.5	>100	>100	75.1
8a	4-OCH_3	52	>100	>100	71.9
8b	2-OCH_3	>100	>100	>100	>100
9a	4-OCH_3	43.9	>100	>100	53.8
9b	2-OCH_3	22.8	>100	>100	>100
10		26.9	>100	>100	64
11		24.7	83.2	89.3	>100

4.1. General method for the preparation of compounds *6*, *7*, *8*, and *9*

To a stirred solution of appropriate acetylenic chalcone **1** or **2** (1 mmol) in ethanol-water mixture and azide **4** or **5** (1 mmol) was added added copper sulphate (0.05 mmol) and sodium ascorbate (0.13 mmol). The reaction mixture was allowed to stir at room temperature for 8 h and the progress was monitored using tlc. After the completion of reaction, water (25 ml) was added and the reaction mixture was extracted twice with dichloromethane (2 × 30 ml). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield a crude product which was purified *via* column chromatography using 50:50 (EtOAc: hexane) mixture.

4.1.1. 1-Cyclohexyl-3(RS)-(4-{2-methoxy-4-[3-(4-methoxyphenyl)-3-oxo-propenyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-azetidin-2-one(*6a*)

Yield 84%; yellow solid; mp120-122 °C; IR ν_{max} (KBr)/cm^{-1}: 1742,1513,1689. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23–1.96 (m, 10H, cyclohexyl H), 3.58 (m, 1H, cyclohexyl H), 3.91 (s, 6H, 2x-OCH_3), 4.72 (dd, 5.1 Hz, 8.7 Hz, 1H, H^b), 5.33 (s, 2H, $-OCH_2-$), 5.65 (dd, 8.7 Hz, 15.6 Hz, 1H, H^c), 5.99 (d, 5.1 Hz, 1H, H^a), 6.64(d, 15.6 Hz, 1H, H^d), 6.93–7.26(m, 10H, −ArH), 7.36(d, 15.6 Hz, 1H, H^e), 7.69 (d, 15.6 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H) 8.03 (d, 9.0 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 22.4, 27.4, 30.9, 47.5, 50.2, 55.9, 56.0, 65.3, 72.5, 113.0, 114.5, 115.3, 116.2, 118.6, 123.4,124.5 126.1, 127.3, 128.2, 128.4, 129.2, 130.6, 132.3, 134.9, 142.9, 145.3, 146.7, 147.8, 166.9, 172.3, 186.9. MS *m*/*z* 619 $(M)^+$. Analysis calculated for $C_{37}H_{38}N_4O_5$: C, 71.82; H, 6.19; N, 9.06. Found: C, 71.79; H, 6.15; N, 9.02.

4.1.2. 1-Cyclohexyl-3(RS)-(4-{4-[3-(2,4-dimethoxy-phenyl)-3-oxo-propenyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-azetidin-2-one(*6b*)

Yield 85%; yellow solid; mp 112–114 °C; IR ν_{max} (KBr)/cm^{-1}: 1738, 1520, 1688. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09–1.96 (m, 10H, cyclohexyl ring), 3.56 (m, 1H, cyclohexyl ring), 3.90 (s, 9H, 3 $-OCH_3$), 4.71 (dd, 5.4 Hz, 8.4 Hz, 1H, H^b), 5.34(s, 2H, $-OCH_2-$), 5.66 (dd, 8.4 Hz, 15.9 Hz, 1H, H^c), 5.97 (d, 5.4 Hz, 1H, H^a), 6.65 (d, 15.9 Hz, 1H, H^d), 6.92–7.28 (m, 9H, −ArH), 7.36 (d, 15.6 Hz, 1H, H^e), 7.69 (d, 15.6 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H) 8.04 (d, 8.7 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 22.3, 27.5, 31.0, 47.6, 51.0, 55.2, 55.9, 56.2, 65.4, 72.5, 102.0, 105.1, 113.1, 114.7, 115.7, 117.7, 123.3, 126.0, 127.3, 124.5, 127.0, 128.5, 129.2, 131.3, 131.0, 135.6, 143.1, 145.2, 146.7, 147.7, 165.8, 167.3, 172.4, 186.9. MS *m*/*z* 649 $(M)^+$. Analysis calculated for $C_{38}H_{40}N_4O_6$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.47; H, 6.33; N,8.60.

4.1.3. 1-Cyclohexyl-3(RS)-{4-[2-methoxy-4-(3-oxo-3-phenyl-propenyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-4(SR)-styryl-azetidin-2-one (*6c*)

Yield 78%; yellow solid; mp 113–115 °C; IR ν_{max} (KBr)/cm^{-1}: 1745,1584,1692. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23–1.99 (m, 10H, cyclohexyl ring), 3.58 (m, 1H, cyclohexyl ring), 3.91 (s, 3H, $-OCH_3$), 4.73 (dd, 5.1 Hz, 9.0 Hz, 1H, H^b), 5.33 (s, 2H, $-OCH_2-$), 5.64 (dd, 9.0 Hz, 15.3 Hz, 1H, H^c), 5.98 (d, 5.1 Hz, 1H, H^a), 6.64(d, 15.3 Hz, 1H, H^d), 6.93–7.26(m, 11H, −ArH), 7.36(d, 15.6 Hz, 1H, H^e), 7.68 (d,

15.6 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H) 8.01 (d, 7.5 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 22.4, 27.4, 30.9, 47.5, 50.2, 55.9, 65.3, 72.5, 113.0, 114.6, 115.3, 118.6, 121.5, 123.4, 124.4, 126.1, 127.3, 128.2, 128.4, 129.2, 130.6, 132.4, 134.2, 134.9, 142.9, 145.3, 146.6, 147.9, 172.3, 187.2. MS *m*/*z* 619 $(M)^+$. Analysis calculated for $C_{36}H_{36}N_4O_4$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.49; H, 6.26; N, 9.47.

*4.1.4. 3(RS)-(4-{2-Methoxy-4-[3-(4-methoxy-phenyl)-3-oxo-propenyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-1-p-tolyl-azetidin-2-one(**7a**)*

Yield 83%; yellow solid; mp 137–139 °C; IR ν_{max} (KBr)/cm^{-1}:1752, 1517, 1693. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, $-CH_3$), 3.91 (s, 6H, 2x$-OCH_3$), 5.19 (dd, 4.5 Hz, 7.8 Hz, 1H, H^b), 5.24 (s, 2H, $-OCH_2-$), 5.81 (dd, 7.5 Hz, 15.6 Hz, 1H, H^c), 6.25 (d, 4.5 Hz, 1H, H^a), 6.72 (d, 15.6 Hz, 1H, H^d), 6.93–7.26 (m, 14H, −ArH), 7.36 (d, 15.6 Hz, 1H, H^e), 7.69 (d, 15.6 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H) 8.03 (d, 9.0 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 20.9, 50.6, 55.9, 56.2, 65.4, 72.4, 113.3, 114.6, 115.4, 117.8, 121.3, 123.1, 124.3, 126.2, 127.6, 128.1, 128.7, 129.0, 129.3, 130.8, 131.2, 132.3, 133.6, 135.1, 138.6, 143.4, 145.6, 146.6, 147.8, 166.9, 172.2, 186.8. MS *m*/*z* 627 $(M)^+$. Analysis calculated for $C_{38}H_{34}N_4O_5$: C, 71.82; H, 6.19; N, 9.06. Found: C, 71.93; H, 6.08; N, 9.00.

*4.1.5. 3(RS)-(4-{4-[3-(2,4-Dimethoxy-phenyl)-3-oxo-propenyl]-2-methoxy-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-1-p-tolyl-azetidin-2-one(**7b**)*

Yield 80%; yellow solid; mp 133–135 °C; IR ν_{max} (KBr)/cm^{-1}: 1750, 1521, 1692. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, $-CH_3$), 3.90 (s, 9H, 3x$-OCH_3$), 5.17 (dd, 5.1 Hz, 7.8 Hz, 1H, H^b), 5.25 (s, 2H, $-OCH_2-$), 5.80 (dd, 7.8 Hz, 15.9 Hz, 1H, H^c), 6.23 (d, 5.1 Hz, 1H, H^a), 6.72 (d, 15.9 Hz, 1H, H^d), 6.91–7.25(m, 13H, −ArH), 7.36 (d, 15.6 Hz, 1H, H^e), 7.69 (d, 15.6 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H) 8.02 (d, 8.7 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 21.0, 50.3, 55.7, 56.1, 56.7, 65.3, 72.5, 101.3, 107.3, 112.9, 113.6, 116.1, 118.4, 119.8, 122.3, 123.5, 124.2, 127.4, 128.1, 128.5, 129.3, 129.5, 131.1, 132.4, 133.6, 135.8, 137.4, 143.8, 144.9, 146.8, 148.5, 165.9, 167.5, 172.2, 187.0. MS *m*/*z* 657 $(M)^+$. Analysis calculated for $C_{39}H_{36}N_4O_6$: C, 71.33; H, 5.53; N, 8.53. Found: C, 71.47; H, 5.58; N, 8.40.

*4.1.6. 3(RS)-{4-[2-Methoxy-4-(3-oxo-3-phenyl-propenyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-4(SR)-styryl-1-p-tolyl-azetidin-2-one(**7c**)*

Yield 83%; yellow solid; mp 142–144 °C; IR ν_{max} (KBr)/cm^{-1}: 1752, 1513, 1688. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, $-CH_3$), 3.90 (s, 3H, $-OCH_3$), 5.19 (dd, 5.7 Hz, 7.5 Hz, 1H, H^b), 5.23 (s, 2H, $-OCH_2-$), 5.81 (dd, 7.5 Hz, 15.9 Hz, 1H, H^c), 6.25 (d, 5.7 Hz, 1H, H^a), 6.71 (d, 15.9 Hz, 1H, H^d), 6.91–7.25 (m, 15H, −ArH), 7.35 (d, 15.6 Hz, 1H, H^e), 7.67 (d, 15.6 Hz, 1H, H^f), 7.82 (s, 1H, triazole-H) 8.03 (d, 8.7 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz), 21.0, 49.8, 56.0, 66.4, 72.5, 113.1, 115.0, 115.4, 117.9, 119.2, 121.3, 123.3, 124.4127.1, 127.3, 128.0, 128.6, 129.1, 129.3, 130.6, 131.4, 134.1, 134.5, 134.9, 137.6, 141.9, 145.3, 146.5, 147.0, 171.7, 187.05. MS *m*/*z* 597 $(M)^+$. Analysis calculated for $C_{37}H_{32}N_4O_4$: C, 74.48; H, 5.41; N, 9.39. Found: C, 74.57; H, 5.29; N, 9.51.

*4.1.7. 1-Cyclohexyl-3(RS)-(4-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-azetidin-2-one(**8a**)*

Yield 78%; Yellow solid; mp 132–134 °C; IR ν_{max} (KBr)/cm^{-1}:1743,1577,1688. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28–1.97 (m, 10H, cyclohexyl H), 3.57 (m, 1H, cyclohexyl H), 3.86 (s, 3H, -OCH_3), 4.75 (dd,5.4 Hz, 8.4 Hz, 1H, H^b), 5.31 (s, 2H, $-OCH_2-$), 5.66 (dd, 8.4 Hz, 15.9 Hz, 1H, H^c), 5.96 (d, 5.4 Hz, 1H, H^a), 6.66(d, 15.9 Hz, 1H, H^d),6.92–7.26(m, 9H, −ArH), 7.39 (d, 15.3 Hz, 1H, H^e), 7.60 (d, 8.4 Hz, 2H, −ArH),7.69 (d, 15.3 Hz, 1H, H^f), 7.79 (s, 1H, triazole-H), 7.96 (d, 8.4 Hz, 2H, −ArH), ^{13}C NMR ($CDCl_3$, 75 Hz): 22.3, 27.4, 30.8, 47.5, 50.1, 55.9, 65.3, 72.4, 113.0, 114.6, 115.3, 118.6, 123.4, 126.1, 127.4, 128.2, 128.4, 129.1, 130.5, 132.4, 134.9, 142.8, 145.2, 147.6, 146.9, 163.2, 172.3, 186.9. MS *m*/*z* 619 $(M)^+$. Analysis calculated for $C_{36}H_{36}N_4O_4$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.61; H, 6.26; N, 9.42.

*4.1.8. 1-Cyclohexyl-3(RS)-(4-{4-[3-(2-methoxy-phenyl)-acryloyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-azetidin-2-one(**8b**)*

Yield 80%; yellow solid; mp 127–129 °C; IR ν_{max} (KBr)/cm^{-1}: 1735, 1523, 1689. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09–1.98 (m, 10H, cyclohexyl H), 3.56 (m, 1H, cyclohexyl H), 3.91 (s, 3H, $-OCH_3$), 4.75 (dd, 5.1 Hz, 8.7 Hz, 1H, H^b), 5.31 (s, 2H, $-OCH_2-$), 5.66 (dd, 8.7 Hz, 15.9 Hz, 1H, H^c), 5.95 (d, 5.1 Hz, 1H, H^a), 6.60 (d, 15.9 Hz, 1H, H^d), 6.85–7.40 (m, 9H, −ArH), 7.39 (d, 15.9 Hz, 1H, H^e), 7.60 (d, 7.5 Hz, 2H, −ArH), 7.79 (s, 1H, triazole-H), 7.96 (d, 7.5 Hz, 2H, −ArH),8.09 (d, 15.9 Hz, 1H, H^f), ^{13}C NMR ($CDCl_3$,75 Hz): 22.4, 27.4, 30.9, 47.4, 50.2, 55.9, 65.2, 72.4, 113.0, 114.6, 115.3, 118.6, 121.5, 121.7, 123.4, 126.1, 127.3, 128.2, 128.4, 129.1, 130.6, 132.4, 134.9, 142.9, 145.3, 147.6, 146.9, 158.8, 172.3, 186.8. MS *m*/*z* 589 $(M)^+$. Analysis calculated for $C_{36}H_{36}N_4O_4$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.51; H, 6.07; N, 9.41.

*4.1.9. 3(RS)-(4-{4-[3-(4-Methoxy-phenyl)-acryloyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-1-p-tolyl-azetidin-2-one(**9a**)*

Yield 80%; Yellow solid; mp 136–138 °C; IR ν_{max} (KBr)/cm^{-1}: 1750,1527,1689. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, -CH_3), 3.90 (s, 3H, $-OCH_3$), 5.17 (dd, 5.4 Hz, 8.7 Hz, 1H, H^b), 5.24 (s, 2H, $-OCH_2-$), 5.80 (dd, 8.7 Hz, 15.9 Hz, 1H, H^c), 6.26 (d, 5.4 Hz, 1H, H^a), 6.70 (d, 15.9 Hz, 1H, H^d), 6.92–7.42 (m, 15H, −ArH), 7.59 (d, 15.9 Hz, 1H, H^e), 7.83 (s, 1H, triazole-H) 7.94 (d, 8.7 Hz, 2H, −ArH), 8.09 (d, 15.9 Hz, 1H, H^f), ^{13}C NMR ($CDCl_3$, 75 Hz), 20.7, 50.5, 55.9, 65.2, 72.5, 112.9, 115.0, 115.2, 117.7, 121.2, 122.4, 125.8, 126.7, 128.0, 128.6, 129.3, 129.6, 131.5, 132.7, 134.1, 134.9, 136.7, 143.9, 146.1, 147.6, 149.1, 167.3, 172.3, 186.3. MS *m*/*z* 597 $(M)^+$. Analysis calculated for $C_{37}H_{32}N_4O_4$: C, 74.48; H, 5.41; N, 9.39. Found: C, 74.61; H, 5.56; N, 9.50.

*4.1.10. 3(RS)-(4-{4-[3-(2-Methoxy-phenyl)-acryloyl]-phenoxymethyl}-[1,2,3]triazol-1-yl)-4(SR)-styryl-1-p-tolyl-azetidin-2-one(**9b**)*

Yield 78%; yellow solid; mp 140–142 °C; IR ν_{max} (KBr)/cm^{-1}: 1752, 1517, 1691. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H, $-CH_3$), 3.91 (s, 3H, $-OCH_3$), 5.16 (dd, 5.4 Hz, 8.7 Hz, 1H, H^b), 5.25 (s, 2H, $-OCH_2-$), 5.80 (dd, 8.7 Hz, 15.9 Hz, 1H, H^c), 6.25 (d, 5.4 Hz, 1H, H^a), 6.71 (d, 15.9 Hz, 1H, H^d), 6.93–7.40 (m, 15H, −ArH), 7.58 (d, 15.6 Hz, 1H, H^e), 7.83 (s, 1H, triazole-H) 7.93 (d, 8.7 Hz, 2H, −ArH), 8.10 (d, 15.9 Hz, 1H, H^f), ^{13}C NMR ($CDCl_3$, 75 Hz), 20.7, 49.8, 55.7, 65.3, 72.5, 113.0, 114.4, 116.0, 117.4, 121.3, 123.2, 124.6, 125.8, 127.4, 128.1, 128.6, 129.5, 130.4, 130.8, 132.5, 134.3, 133.6, 135.0, 137.3, 141.8, 144.6, 147.6, 147.9, 166.8, 172.6, 187.1. MS *m*/*z* 597 $(M)^+$. Analysis calculated for $C_{37}H_{32}N_4O_4$: C, 74.48; H, 5.41; N, 9.39. Found: C, 74.61; H, 5.33; N, 9.47.

*4.1.11. 4-[1-(1-Cyclohexyl-2-oxo-4(SR)-styryl-azetidin-3(RS)-yl)-1H-[1,2,3]triazol-4-ylmethoxy]-3-methoxy-benzaldehyde(**10**)*

Yield 80%; white solid; mp 155–156 °C; IR ν_{max} (KBr)/cm^{-1}: 1735, 1523, 1689. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09–1.96 (m, 10H, cyclohexyl ring), 3.57 (m, 1H, cyclohexyl ring), 3.90 (s, 3H, $-OCH_3$), 4.73 (dd, 5.1 Hz, 8.7 Hz, 1H, H^b), 5.36 (s, 2H, $-OCH_2-$), 5.65 (dd, 8.7 Hz, 15.6 Hz, 1H, H^c), 5.90 (d, 5.1 Hz, 1H, H^a), 6.62 (d, 15.6 Hz, 1H, H^d), 7.06–7.25 (m, 7H, −ArH), 7.38 (s, 1H, −ArH), 7.79 (s, 1H, triazole-H), 9.78 (s, 1H, −CHO), ^{13}C NMR ($CDCl_3$, 75 Hz): 22.3, 27.3, 30.9, 47.5, 50.2, 56.4, 66.4, 72.5, 115.2, 116.8, 123.0, 123.3, 126.3,

127.2, 127.4, 128.4, 130.0, 132.4, 135.2, 145.3, 148.3, 152.2, 172.8, 189.9. MS *m/z* 487 $(M)^+$. Analysis calculated for $C_{28}H_{30}N_4O_4$: C, 69.12; H, 6.21; N, 11.51. Found: C, 69.00; H, 6.31; N, 11.40.

*4.1.12. 3-Methoxy-4-[1-(2-oxo-4(SR)-styryl-1-p-tolyl-azetidin-3(RS)-yl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehydeYield (**11**)*

78%; Yellow solid; mp 140–142 °C; IR ν_{max} (KBr)/cm^{-1}: 1752, 1517, 1691. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.30 (s, 3H, $-CH_3$), 3.90 (s, 3H, $-OCH_3$), 5.16 (dd, 5.4 Hz, 8.4 Hz, 1H, H^b), 5.25 (s, 2H, $-OCH_2-$), 5.80 (dd, 8.4 Hz, 15.9 Hz, 1H, H^c), 6.25 (d, 5.4 Hz, 1H, H^a), 6.71(d, 15.9 Hz, 1H, H^d), 6.93–7.25 (m, 11H, –ArH), 7.37 (s, 1H, –ArH), 7.82 (s, 1H, triazole-H), 9.80 (s, 1H, –CHO), ^{13}C NMR ($CDCl_3$, 75 Hz), 20.3, 54.8, 56.4, 65.7, 72.3, 115.3, 115.7, 119.8, 122.2, 123.6, 125.6, 126.4, 127.3, 127.7, 128.0, 128.9, 129.5, 131.7, 133.4, 136.1, 144.5, 147.9, 152.2, 171.3, 189.9. MS *m/z* 495 $(M)^+$. Analysis calculated for $C_{29}H_{26}N_4O_4$: C, 70.43; H, 5.30; N, 11.33. Found: C, 70.57; H, 5.41; N, 11.37.

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