SYNTHESIS OF THIAZOLIDINE-CARBAZOLE LINKED 1,2,3-TRIAZOLE HYBRIDS AND THEIR ANTI-CANCER EVALUATION

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ABSTRACT

Here we described the synthesis of novel 1,2,3-triazole linked thiazolidine-2,4-dione and carbazole derivatives and screened for their anticancer activities against three human cancer cell lines, MCF-7, HeLa and SKOV3 using MTT assay. The newly synthesized triazole hybrids are characterized using ¹H NMR, ¹³C NMR, IR and Mass spectral data. The results indicated that the most potent compound in this series is compound 3b against MCF-7, compound 3i against HeLa and compound 3d against SKOV3, which showed the highest activity with IC₅₀ value of 32.92 µg/ml, 12.08 µg/ml and 29.06 µg/ml respectively.

Keywords: 1,2,3-triazole, Carbazole, Thiazolidine-2,4-dione, Anticancer Activity

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INTRODUCTION

In the recent era of medicinal chemistry, a unique pharmacophore with the combination of two lead moieties is the usual application to obtain bioactive hybrid compounds with novelty and high active that have attributed a new prospect in multifactorial disease therapeutics. In this molecular hybridization concept, the compounds obtained may be due to binding of multiple copies of the same (homo) or unique (hetero) ligands connected via linkers or a scaffold, are reported to act by inhibiting two or more conventional targets simultaneously. Regarding heterobivalent ligands, the hybrid compound is composed of two different pharmacophores and this characteristic in targeting different protein molecules or two specific sites on the same protein target. The choice of and concurrent binding of heterobivalent ligands to various targets could be beneficial for the treatment of many diseases including cancer.¹ Cancer, due to which massive *human* deaths occur all through the world. By the year 2020, the approximation of cancer occurrence per year is 16 million new cases and more than 20% of the population is affected by cancer with increasing incidence annually.^{2,3} Granting all this, the exploration of anticancer drugs has been remarkable research, advancing attempts for the improvement of chemicals that might be advantageous in the chemotherapy of cancer. Thiazolidinediones (TZDs), considering the governance of various physiological processes, have been accountable in the wide-ranging scientific research field. Thiazolidinediones constitutes some important drugs that includes rosiglitazone, pioglitazone, ciglitazone and troglitazone. On the other hand, glitazones have been outlined in recent times due to their peculiar anticancer effect mechanisms.⁴ In the past years, these compounds have been well-established with their various functioning biological activities of antimicrobial, antimalarial, anti-inflammatory, anticancer and antihyperlipidemic, antihyperglycemic, cholesterol esterase inhibitor, 15-hydroxyprostaglandin

dehydrogenase(15-PGDH) inhibitor and bacterial arylamine N-Acetyltransferases (NATs) inhibitor.⁵⁻¹⁵ On the other hand, carbazoles and their derivatives attained great significance for medicinal chemists for the reason that they possess various biological activities. Carbazole is an aromatic heterocyclic organic compound found in distinct natural products and drug molecules. This carbazole framework illustrates a vast range of biological and pharmacological activities inclusive of antibacterial, anti-inflammatory, anticancer, antitubercular, antidiabetic, antioxidant, anti-HIV and inhibitors of topoisomerase II.¹⁶⁻²⁴ A few carbazole derivatives are having probable multifunctional agents for the treatment of neurological disorders.²⁵ Some of the acclaimed thiazolidine-2,4-dione and carbazole derivatives were described to be pharmacological active agents as represented in Fig.-1.

Fig.-1: Some of the Selected Molecules that containingThiazolidine-2,4-dione and Carbazole Derivatives with Pharmacological Activity

EXPERIMENTAL

General Information

S.D. Fine Chemicals are used without purification. For thin-layer chromatography Merck silica gel 60F-254 pre-coated plates were used and for column chromatography silica gel 60–120 mesh was used. Casia-Siamia (VMP-AM) melting point apparatus was used for reading melting points. ¹H and ¹³C NMR spectra were measured on 400 MHz and 100 MHz spectrometers respectively, using DMSO-d₆ as a solvent and TMS as a reference. Shimadzu QP5050A quadrupole-based mass spectrometer was used for recording mass spectrum.

Synthesis of 5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione (1)

9-ethyl-9H-carbazole-3-carbaldehyde (30 mmol) was taken in toluene and to this thiazolidine-2,4-dione (30 mmol) and piperidine was added and refluxed for four hours. After completion of the reaction as indicated by TLC the round bottom flask was cooled to 25 °C and it was recrystallized from water to get compound 1.

Synthesis of 5-((9-ethyl-9H-carbazol-3-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione(2)

5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione (23.60 mmol) was dissolved in 10 mL of acetone solvent and K₂CO₃ (22 mmol) was used as base. After 10 minutes 3-bromoprop-1-yne (23 mmol) was added and the reaction mixture refluxed for 3 hours and after completion of the reaction which was known by TLC, it was extracted with ethyl acetate to get 5-((9-ethyl-9H-carbazol-3-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione(2). It was purified by column chromatography over silica gel (100-200 mesh) in 10% ethyl acetate in hexane to get compound 2 in pure state.

Mp. 180-182°C. Yield 91%. ¹HNMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 1.7 Hz, 1H), 8.12 (t, *J* = 3.6 Hz, 2H), 7.59 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.44 (dd, *J* = 8.4, 3.7 Hz, 2H), 7.33 – 7.29 (m, 1H), 4.50 (d, *J* = 2.5 Hz, 2H), 4.37 (q, *J* = 7.3 Hz, 2H), 2.28 (t, *J* = 2.5 Hz, 1H), 1.45 (t, *J* = 7.3 Hz, 3H).

Synthesis of 1,2,3-triazole ring linked 5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione hybrids 3a-3k

Compound **2** (1.0 mmol) and aromatic azides (1.0 mmol) were dissolved in tetrahydrofuran solvent (10 mL) and copper iodide (10 mol%) was added. The reaction was maintained for 12 h at room temperature. After completion of the reaction which was confirmed by TLC, the solvent was removed and extracted with DCM. The organic layers were dried using anhydrous sodium sulphate and concentrated to get the final products **3a-3k**.

5-((9-ethyl-9H-carbazol-3-yl)methylene)-3-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl) thiazolidine-2,4-dione (3a)

Yield 81%, mp 150-152 °C. IR spectrum, ν , cm^{-1} : 3155, 2923, 1733, 1675, 1585, 1456. ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.80 (s, 1H), 7.69 – 7.61 (m, 2H), 7.57 (s, 1H), 7.54 (s, 1H), 7.45 – 7.34 (m, 2H), 7.30 – 7.18 (m, 5H), 7.04 (s, 1H), 5.08 (s, 2H), 4.38 (q, $J = 7.2$ Hz, 2H), 1.46 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 165.2, 143.0, 140.5, 140.1, 136.1, 135.1, 130.7, 129.9, 127.8, 126.8, 123.5, 122.8, 121.9, 121.8, 121.5, 120.6, 119.9, 119.8, 116.5, 110.9, 109.5, 37.2, 36.5, 13.7. ESI-MS: m/z 480 ($M+1$) observed for $\text{C}_{27}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$.

5-((9-ethyl-9H-carbazol-3-yl)methylene)-3-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione(3b)

Yield 83%, mp 162-163 °C. IR spectrum, ν , cm^{-1} : 3154, 2923, 1733, 1675, 1585, 1456. ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, $J = 7.4$ Hz, 2H), 7.99 (s, 1H), 7.93 (d, $J = 7.4$ Hz, 2H), 7.80 (s, 1H), 7.57 (s, 1H), 7.53 (s, 1H), 7.44 – 7.36 (m, 2H), 7.29 – 7.19 (m, 3H), 4.88 (s, 2H), 4.38 (q, $J = 7.2$ Hz, 2H), 1.47 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 165.9, 146.1, 140.6, 140.1, 135.6, 134.9, 132.7, 127.8, 126.8, 1233.7, 123.5, 122.8, 121.9, 121.8, 121.7, 121.3, 120.7, 119.8, 116.6, 110.1, 109.7, 37.2, 36.5, 13.7. ESI-MS: m/z 525 ($M+1$) observed for $\text{C}_{27}\text{H}_{20}\text{N}_6\text{O}_4\text{S}$.

3-((1-(4-acetylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione (3c)

Yield 80%, mp 155-158 °C. IR spectrum, ν , cm^{-1} : 3129, 2940, 1725, 1655, 1550, 1439. ^1H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.47 (s, 1H), 8.25 (s, 1H), 8.18 – 8.08 (m, 4H), 7.91 – 7.58 (m, 4H), 7.54 (s, 1H), 7.30 (s, 1H), 5.05 (s, 2H), 4.50 (q, 2H), 2.63 (s, 3H), 1.35 (t, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.9, 167.3, 165.3, 143.0, 140.6, 140.1, 139.4, 136.4, 134.9, 132.8, 130.0, 127.81, 126.7, 123.7, 123.6, 122.9, 121.9, 120.8, 119.9, 119.7, 116.6, 110.1, 109.7, 37.2, 36.5, 26.8, 13.7. ESI-MS: m/z 524 ($M+1$) observed for $\text{C}_{28}\text{H}_{21}\text{N}_5\text{O}_4\text{S}$.

3-((1-[3,4-dichlorophenyl]-1H-1,2,3-triazol-4-yl)methyl)-5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione(3d)

Yield 82%, mp 132-134 °C. IR spectrum, ν , cm^{-1} : 3156, 2920, 1733, 1683, 1518, 1488. ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.46 (s, 1H), 8.34 – 8.20 (m, 2H), 8.19 – 8.09 (m, 1H), 8.02 – 7.91 (m, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 7.74 – 7.75 (m, 1H), 7.71 (dd, $J = 16.1, 8.1$ Hz, 2H), 7.54 (t, $J = 7.3$ Hz, 1H), 7.30 (t, $J = 7.3$ Hz, 1H), 5.03 (s, 2H), 4.49 (q, $J = 6.7$ Hz, 2H), 1.34 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 165.2, 142.9, 140.6, 140.1, 135.9, 135.0, 132.2, 131.7, 131.0, 127.8, 126.7, 123.7, 123.5, 122.8, 121.9, 121.8, 121.6, 120.7, 119.9, 119.8, 116.5, 110.9, 109.7, 37.2, 36.5, 13.71. ESI-MS: m/z 548 ($M+1$) observed for $\text{C}_{27}\text{H}_{19}\text{Cl}_2\text{N}_5\text{O}_2\text{S}$.

5-((9-ethyl-9H-carbazol-3-yl)methylene)-3-((1-(2-ethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)thiazolidine-2,4-dione(3e)

Yield 78%, mp 130-132 °C. IR spectrum, ν , cm^{-1} : 3155, 2923, 1733, 1675, 1585, 1456. ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.45 (s, 1H), 8.25 (d, $J = 7.7$ Hz, 1H), 8.14 (s, 1H), 7.78 (d, $J = 8.6$ Hz, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.68 (d, $J = 8.2$ Hz, 1H), 7.57 – 7.47 (m, 3H), 7.46 – 7.34 (m, 2H), 7.30 (t, $J = 7.4$ Hz, 1H), 5.06 (s, 2H), 4.48 (q, $J = 7.1$ Hz, 2H), 2.43 (q, $J = 7.4$ Hz, 2H), 1.34 (t, $J = 6.9$ Hz, 3H), 1.01 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 165.3, 140.5, 140.1, 139.2, 135.5,

134.9, 130.2, 129.8, 127.8, 126.9, 126.7, 126.3, 125.5, 123.6, 123.4, 123.5, 122.9, 121.8, 120.8, 119.9, 116.6, 110.1, 109.7, 37.3, 36.5, 23.7, 14.8, 13.7. ESI-MS: m/z 508 (M+1) observed for $C_{29}H_{25}N_5O_2S$.

5-{(9-ethyl-9H-carbazol-3-yl)methylene}-3-{{[1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl]methyl}thiazolidine-2,4-dione (3f)}

Yield 80%, mp 125-127 °C. IR spectrum, ν , cm^{-1} : 3156, 2920, 1733, 1683, 1518, 1488. 1H NMR (400 MHz, DMSO- d_6) δ 8.07 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.70 – 7.65 (m, 2H), 7.52 (s, 1H), 7.42 – 7.34 (m, 2H), 7.29 (dd, J = 5.1, 2.4 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.15 – 7.09 (m, 2H), 4.98 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). ESI-MS: m/z 498 (M+1) observed for $C_{27}H_{20}FN_5O_2S$.

3-{{[1-[4-chlorophenyl]-1H-1,2,3-triazol-4-yl]methyl}-5-{{(9-ethyl-9H-carbazol-3-yl)methylene}thiazolidine-2,4-dione (3g)}

Yield 85%, mp 135-138 °C. IR spectrum, ν , cm^{-1} : 3156, 2920, 1733, 1683, 1518, 1488. 1H NMR (400 MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.46 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.78 – 7.58 (m, 3H), 7.54 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 5.03 (s, 2H), 4.49 (d, J = 6.7 Hz, 2H), 1.34 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 167.2, 165.2, 142.9, 140.6, 140.1, 136.0, 135.0, 130.6, 129.9, 127.7, 126.7, 123.5, 122.8, 121.9, 121.8, 121.6, 120.7, 119.9, 119.8, 116.5, 110.9, 109.6, 37.2, 36.4, 13.7. ESI-MS: m/z 514 (M+1) observed for $C_{27}H_{20}ClN_5O_2S$.

3-{{[1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl]methyl}-5-{{(9-ethyl-9H-carbazol-3-yl)methylene}thiazolidine-2,4-dione (3h)}

Yield 80%, mp 120-122 °C. 1H NMR (400 MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.46 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 7.89 (d, J = 8.3 Hz, 2H), 7.84 – 7.76 (m, 3H), 7.71 (dd, J = 16.8, 8.3 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 5.03 (s, 2H), 4.49 (q, J = 6.7 Hz, 2H), 1.34 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 167.2, 165.3, 140.6, 140.1, 135.6, 134.9, 132.7, 127.8, 126.7, 123.7, 123.5, 122.9, 121.9, 121.9, 121.7, 121.5, 121.3, 120.8, 119.9, 116.6, 110.1, 109.7, 37.2, 36.5, 13.7. ESI-MS: m/z 558 (M+1) observed for $C_{27}H_{20}BrN_5O_2S$.

5-{{(9-ethyl-9H-carbazol-3-yl)methylene}-3-{{[1-[4-methoxyphenyl]-1H-1,2,3-triazol-4-yl]methyl}thiazolidine-2,4-dione (3i)}

Yield 75%, mp 130-133 °C. IR spectrum, ν , cm^{-1} : 3156, 2926, 1736, 1685, 1588, 1451. 1H NMR (400 MHz, DMSO- d_6) δ 8.08 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.64 – 7.59 (m, 2H), 7.52 (s, 1H), 7.42 – 7.21 (m, 7H), 4.88 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.57 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 167.3, 165.3, 156.2, 143.0, 140.6, 140.1, 139.4, 136.3, 134.9, 130.0, 127.8, 126.7, 123.7, 123.5, 122.9, 121.9, 120.8, 119.9, 119.7, 116.6, 110.1, 109.7, 55.1, 37.2, 36.5, 13.7. ESI-MS: m/z 510 (M+1) observed for $C_{27}H_{23}N_5O_3S$.

5-{{[1-(9-ethyl-9H-carbazol-3-yl)methylene]-3-{{[1-hexyl-1H-1,2,3-triazol-4-yl]methyl}thiazolidine}-2,4-dione (3j)}

Yield 73%, mp 121-123 °C. 1H NMR (400 MHz, DMSO- d_6) δ 7.69 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.43 (s, 1H), 7.32 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 7.19 – 7.08 (m, 2H), 5.02 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.76 (t, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H), 1.36 – 1.23 (m, 8H), 0.88 (t, J = 6.7 Hz, 3H). ESI-MS: m/z 586 (M+1) observed for $C_{27}H_{29}N_5O_2S$.

5-{{(9-ethyl-9H-carbazol-3-yl)methylene}-3-{{[1-octyl-1H-1, 2, 3-triazol-4-yl]methyl}thiazolidine}-2, 4-dione (3k)}

Yield 72%, mp 121-124 °C. IR spectrum, ν , cm^{-1} : 3122, 2924, 1744, 1684, 1591, 1506. 1H NMR (400 MHz, DMSO- d_6) δ 7.62 (s, 1H), 7.61 (s, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 – 7.01 (m, 2H), 5.04 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.76 (t, J = 7.2 Hz, 2H), 1.79 – 1.70 (m, 4H), 1.45 (t, J = 7.2 Hz, 3H), 1.25 – 1.13 (m, 8H), 0.98 (t, J = 6.7 Hz, 3H). ESI-MS: m/z 516 (M+1) observed for $C_{29}H_{33}N_5O_2S$.

RESULTS AND DISCUSSION

Chemistry

We have prepared a series of 5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione linked 1,2,3-triazoles **3a-3k** which was shown in Scheme-1. We have designed the synthesis in three steps. First, 5-((9-ethyl-9H-carbazol-3-yl)methylene)thiazolidine-2,4-dione (**1**) was prepared from 9-ethyl-9H-carbazole-3-carbaldehyde and 2,4-thiazolidinedione using piperidine as a catalyst. Next, compound **1** was propargylated using potassium carbonate as a base in acetone solvent. Finally, the alkyne **2** was reacted with different azides in tetrahydrofuran solvent using copper iodide as a catalyst to get the 1,2,3-triazole.

Scheme-1: Synthesis of Thiazolidine-2,4-dione derivatives **3(a-k)****In-vitro Anti-cancer Screening**

The newly prepared hybrids were screened for in vitro cytotoxic activity based on MTT assay against three human cancer lines MCF-7, HeLa and SKOV3. The various concentrations of the synthetic compounds (final concentration 1, 10, 20, 30, 40 and 50 $\mu\text{g/ml}$) were applied to calculate IC_{50} and they are listed in Table-1. From Table-1 it is evident that compound **3b** against MCF-7, compound **3i** against HeLa and compound **3d** against SKOV3, showed the highest activity with IC_{50} value of 32.92 $\mu\text{g/ml}$, 12.08 $\mu\text{g/ml}$ and 29.06 $\mu\text{g/ml}$ respectively. Doxorubicin was used as a reference for in vitro anticancer screening.

Table-1: Anticancer Activity of Synthesized Compounds

Compound	Anticancer Activity (IC_{50} in μM)		
	MCF-7	HeLa	SKOV3
3a	77.72	17.76	91.78
3b	32.92	42.06	> 100

3c	> 100	33.87	> 100
3d	> 100	57.05	29.06
3e	> 100	32.36	> 100
3f	> 100	62.77	> 100
3g	33.15	20.07	> 100
3h	> 100	24.00	> 100
3i	91.66	12.08	> 100
3j	> 100	28.87	> 100
Doxorubicin	35.29	02.96	11.34

Biological Evaluation

Cytotoxicity Test (MTT Assay)

The MTT assay was used for screening the in vitro anticancer activity of all the synthesized hybrids. Three different cancer cell lines SKOV3, MCF7 and HeLa were obtained from NCL Pune. These cell lines are maintained in Dulbecco's Modified Eagle's Medium where it is added with 10 % Fetal bovine serum followed by 100 U/ml penicillin, 100 µg/ml streptomycin and 2 mM l-glutamine and human body temperature under CO₂ incubator. Then the cells were seeded in 96 well culture plates. After adding the compounds in different concentrations ranging from 1 micromolar to 50 micromolar in triplicates were kept at room temperature for 24 hours. The cancer cells were incubated with MTT for 4hr and 100 microlitre dimethyl sulfoxide was added to each well and the absorbance was measured Synergy H1, the multi-mode plate reader. For this assay doxorubicin was used as a positive control.

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CONCLUSION

Here we demonstrated the synthesis and anti-cancer screening of 1,2,3-triazole linked thiazolidine-carbazole hybrids. The compounds 3b, 3i and 3d are effective in anticancer activity.

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[RJC-6249/2020]