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Synthesis and antimalarial activity of sulfonamide-attached coumarin-[1,2,3]-triazoles

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Drug resistance in malaria parasites is one of the major stumbling blocks hindering the goal of malaria elimination. One of the major strategies to counter drug resistance is the development of new potent antimalarial drugs. In the present study, a series of novel sulfonamide based coumarin-[1,2,3]-triazole conjugates have been synthesized *via* Huisgen reaction between azidosulfonamides and 4-hydroxy- or 7-hydroxymethylcoumarinoalkynes. All the compounds have been characterized spectroscopically and screened for their *in vitro* antimalarial activity against *P. falciparum* 3D7 strain. Out of the twenty five synthesized compounds, four compounds displayed significant activity (IC_{50} <10 μM) with the most active compound having an IC_{50} of 3.64 μM.

Keywords: Antimalarial activity, 4-hydroxycoumarin, 7-hydroxycoumarin, Huisgen [3+2] cycloaddition, sulfonamides, [1,2,3]-triazoles

Malaria is a mosquito-borne parasitological disease prominent in tropical and subtropical regions of the world. It is caused by the parasites of the genus *Plasmodium* (*P.*) and is transmitted by female *Anopheles* mosquitoes. There are five species of malaria parasites that infect humans, namely *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae,* and *P. knowlesi*. Among these, *P. falciparum* is responsible for causing the most lethal form of malaria and the majority of malaria-related mortality and morbidity[1]. *P. falciparum* is gradually becoming resistant to commonly used antimalarial drugs. *P. falciparum* strains occurring in most malaria endemic countries have become completely resistant to the majority of antimalarial drugs including chloroquine, mefloquine, and sulfadoxine/pyrimethamine[1,2]. Moreover, *P. falciparum* strains in the South-East Asia region have already started to show signs of reduced efficacy/partial resistance to the most potent malaria drug of the present era, artemisinin[2]. In the absence of a safe and effective transmission-blocking drug, preventing the widespread transmission of artemisinin-resistant parasites to other areas is extremely challenging and crucial[3-7]. Potential dissemination of artemisinin-resistant parasites outside of South-East Asia, especially to sub-Saharan Africa, where the malaria burden is on the higher side, can have disastrous consequences. Therefore, to tackle the threat of drug resistance and to increase the ammunition against the malaria parasite, researchers worldwide are focused on discovering novel antimalarial drugs with a unique mechanism of action. To this end, our group is routinely involved in synthesizing hybrid antimalarial compounds with multiple pharmacologically significant moieties, including quinoline, triazole, sulfonamide and berberine[8-10]. In continuation with our previous efforts of developing potent sulfonamide based hybrid antimalarials, we have used the sulfonamide moiety as a base for synthesizing novel antimalarials. Sulfonamide is the same moiety present in one of the prominent antimalarial drugs of today, sulfadoxine. Developing drugs based on a sulfonamide moiety is expected to result in compounds with similar cross resistance patterns as sulfadoxine. They would thus illicit drug resistance earlier in areas already harboring sulfadoxine resistance. Therefore, to broaden the structural diversity of the compounds and to delay the onset of drug resistance, sulfonamide moiety is appended to another class of heterocycles, the coumarins (2*H*-chromen-2-ones), by [1,2,3]-triazole linkers to yield prospective antimalarial drug

candidates. Coumarins are an important class of oxygen heterocycles composed of fused benzene and α-pyrone rings. They are released as secondary metabolites during metabolism in bacteria, fungi and plants, and possess a myriad of biological properties including antioxidant[11], antimalarial[12], antitumor[13], antifungal[14], cytotoxic[15], anti-inflammatory[16] antiprotozoal[17], anti-HIV[18], antidiabetic[19], and antiviral properties[20]. Moreover, a naturally occurring 4-phenylcoumarin derivative inophyllum A, which has two fused pyran rings, is reported to be as antitumor and anti-HIV agents[21]. Similarly, other naturally occurring neoflavones (Figure 1) such as coutareagenin, (±)-inophyllum E, apetalolide, interruptin A, and ponnalide also have diverse pharmacological properties[22]. For instance, coutareagenin (5-hydroxy-7-methoxy-4-(3,4-dihydroxyphenyl)-2*H*-benzo-1-pyran-2-one) isolated from the bark of *Hintonia latiflora*, helps in controlling blood sugar levels in diabetic patients[22]. Similarly, [1,2,3]-triazole is another pharmacologically relevant moiety present in various antimalarial[9,10], antifungal[23], antibacterial[24] and antitubercular compounds[25].

Therefore, in the present study, novel chemical entities with three 'biologically privileged' pharmacophores were obtained by the reaction of various coumarinoalkynes with sulfonamide-based azides under click reaction conditions. These compounds were then characterized based on spectroscopic data and evaluated for their antimalarial potential in culture.

Results and Discussion

Synthesis

For the synthesis of desired sulfonamide-appended coumarin-[1,2,3]-triazoles, azides (**1a-e**) were synthesized from the corresponding sulfonamide amines *via* diazotization in the presence of concentrated HCl and sodium nitrite followed by the reaction with NaN_3 according to the literature procedure[26]. On the other hand, the coumarinoalkynes (**3** and **5a-d**) were prepared in good to excellent yields by the reaction of propargyl bromide and commercially available 2*H*-chromen-2-ones in acetone containing K_2CO_3 as a base at 60°C for 8 hours. After chromatographic purification, the respective terminal alkynes were characterized spectroscopically and their spectral data are found in agreement with the reported data[27]. Finally, desired sulfonamide-appended coumarin-[1,2,3]-triazoles (**6a-e, 7a-d, 8a-d, 9a-d, 10a-d**, and **11a-c**) were prepared *via* a Cu(I)-catalyzed Huisgen [3+2] cycloaddition reaction of sulfonamide based azides (**1a-e**) and terminal alkynes of 4-hydroxy and 7-hydroxy coumarins (**3** and **5a-d**) in the presence of sodium ascorbate and $CuSO_4.5H_2O$ in an equimolar mixture of *t*-butanol and water at 50°C for 5 hours (Scheme I).

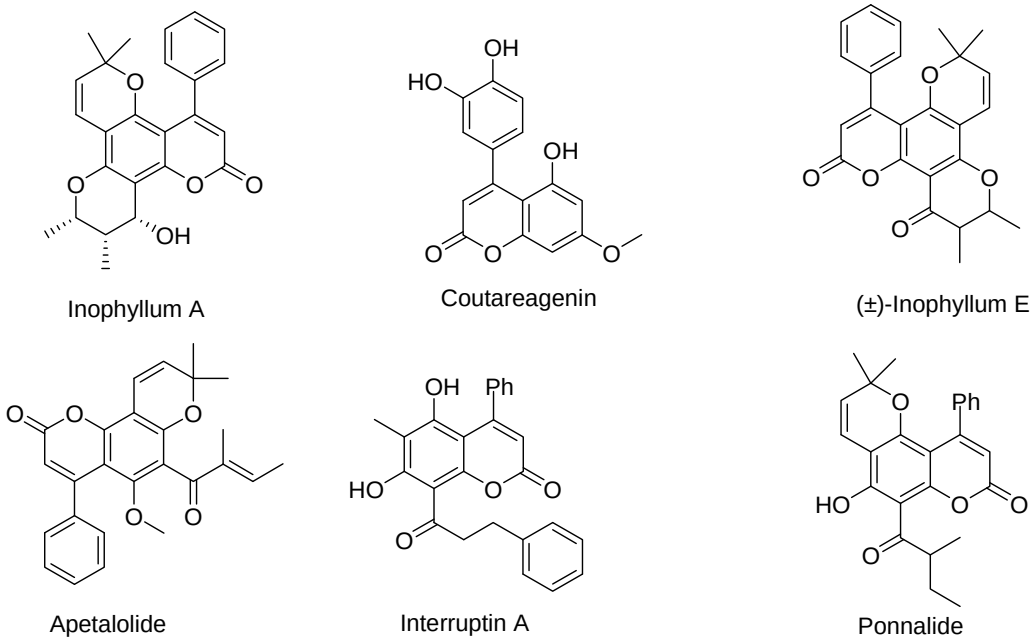
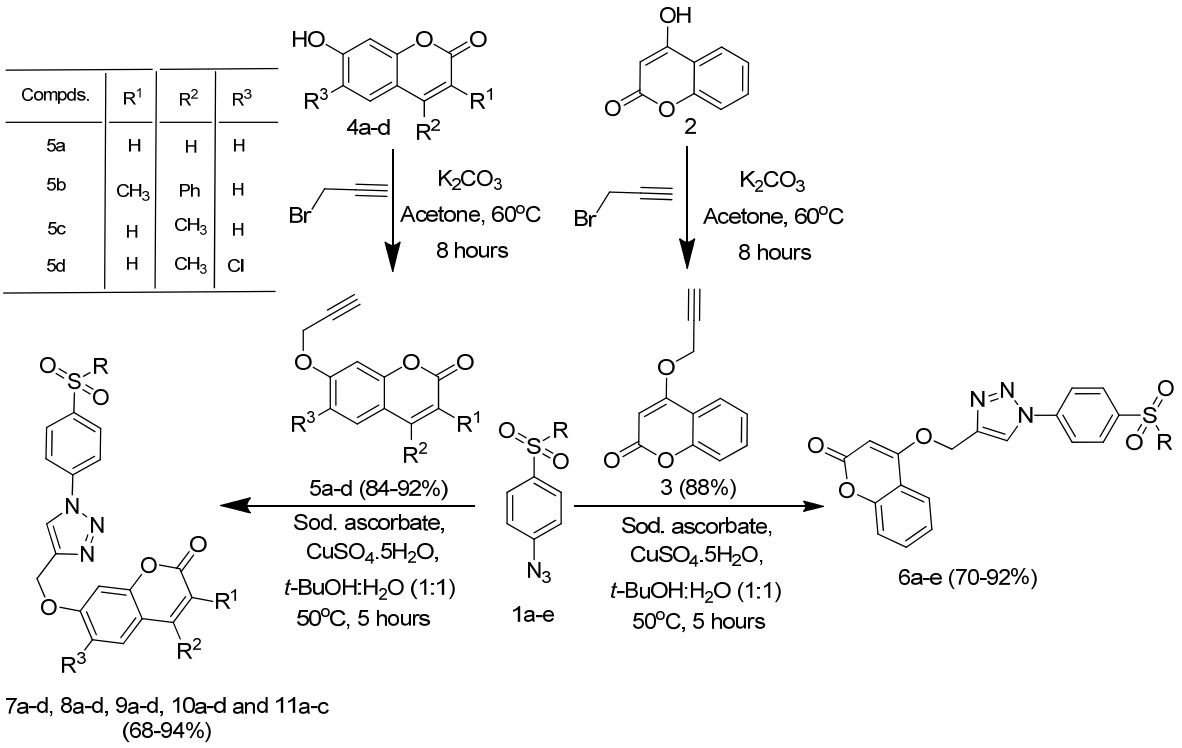


Figure 1 — Structures of some biologically active naturally occurring coumarin derivatives



Scheme I — Synthesis of sulfonamide-attached coumarin-[1,2,3]-triazole hybrids

Biological evaluation

Antimalarial activity evaluation against *P. falciparum* 3D7

Antimalarial activity of the synthesized sulfonamide-appended coumarin-[1,2,3]-triazoles (**6a-e**, **7a-d**, **8a-d**, **9a-d**, **10a-d**, and **11a-c**) was evaluated against 3D7 strain of *P. falciparum* by radioactive [^{3}H] hypoxanthine incorporation inhibition assay as previously described[9]**.** All the tested compounds demonstrated IC_{50} values in the micromolar range (3.64 µM to 100 µM). The most promising compound in terms of antimalarial activity was found to be **7c**, a 1,2,3-triazole bearing primary sulfonamide and 7-hydroxymethyl-4-methyl-2*H*-chromen-2-one moieties (IC_{50} = 3.64 µM). Another primary sulfonamide-appended coumarin-[1,2,3]-triazole hybrid, **7b,** with an IC_{50} value of 3.68 µM was not far behind than the lead compound, **7c**. Among the other hybrid molecules, the [1,2,3]-triazole, **10c** tethered with 7-hydroxy-4-methylcoumarin and a tertiary sulfonamide bearing morpholine scaffold also showed remarkable potency with IC_{50} of 5.18 µM. This was followed by compound **7d** with an IC_{50} value 8.96 µM. The results of *in vitro* antimalarial activity are summarized in Table I.

Materials and Methods

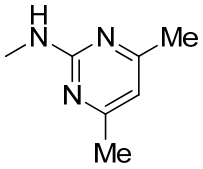
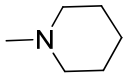
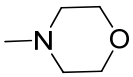
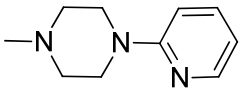
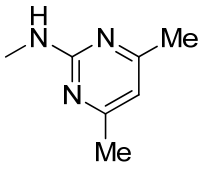
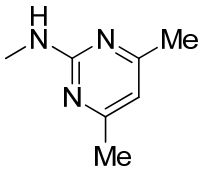
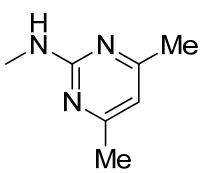
The chemicals and solvents were purchased from Sigma-Aldrich, Merck, Spectrochem and SD Fine Chemicals and used as received without further purification. Thin layer chromatography was performed on silica gel 60 F_{254} (pre-coated aluminium sheets) from Merck. ^{1}H NMR and ^{13}C NMR spectra were recorded either in $CDCl_3$ or in DMSO-d_6, using TMS as an internal standard on Jeol ECX 400 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm), and coupling constants (J) are expressed in Hertz (Hz). Infrared spectra were recorded on Perkin-Elmer IR spectrometer and absorption maxima (ν_{max}) were measured in cm^{-1}. High resolution mass spectra were recorded on Agilent G6530 AA LC-HRMS Q-TOF mass spectrometer. Melting points were recorded in open capillary tubes and are uncorrected.

Experimental Section

General procedure for the synthesis of sulfonamide-coumarin-[1,2,3]-triazoles 6a-e, 7a-d, 8a-d, 9a-d, 10a-d and 11a-c

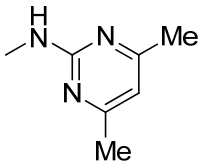
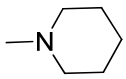
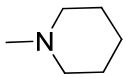
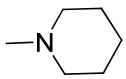
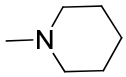
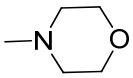
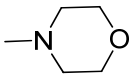
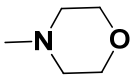
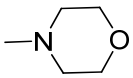
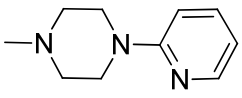
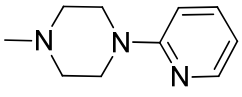
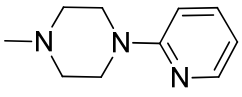
To a well stirred solution of azides (**1a-e**; 1 mmol) and alkynes (**3** and **5a-d**; 1.1 mmol) in *t*-BuOH (4 mL), a solution of sodium ascorbate (0.4 mmol) in water (2 mL) was added. After 10 minutes, a solution of $CuSO_4.5H_2O$ (0.6 mmol) in water (2 mL) was added, and the reaction mixture was stirred at 50°C for 5 hours under an inert atmosphere. On completion

Table I — Isolated yields and *in vitro* antimalarial activity of sulfonamide-appended coumarin-[1,2,3]-triazoles (**6a-e**, **7a-d**, **8a-d**, **9a-d**, **10a-d** and **11a-c**)

Compd	R	R^1	R^2	R^3	Yield* (%)	Antimalarial activity (after 42 h)	
						IC_{50} (μg/mL)	IC_{50} (μM)
6a	NH_2	–	–	–	92	40	100.50
6b		–	–	–	70	>40	>79.36
6c		–	–	–	88	>40	>85.83
6d		–	–	–	85	16	34.18
6e		–	–	–	82	40	73.52
7a	NH_2	H	H	H	90	20	50.25
7b	NH_2	CH_3	Ph	H	82	1.8	3.68
7c	NH_2	H	CH_3	H	94	1.5	3.64
7d	NH_2	H	CH_3	Cl	88	4	8.96
8a		H	H	H	70	>40	>79.36
8b		CH_3	Ph	H	68	>40	>67.34
8c		H	CH_3	H	72	12	20.47

(*Contd.*)

Table I — Isolated yields and *in vitro* antimalarial activity of sulfonamide-appended coumarin-[1,2,3]-triazoles (**6a-e**, **7a-d**, **8a-d**, **9a-d**, **10a-d** and **11a-c**) (*Contd.*)

Compd	R	R^1	R^2	R^3	Yield* (%)	Antimalarial activity (after 42 h)	
						IC_{50} (μg/mL)	IC_{50} (μM)
8d		H	CH_3	Cl	74	10	18.11
9a		H	H	H	85	>40	85.65
9b		CH_3	Ph	H	80	40	71.81
9c		H	CH_3	H	88	28	58.33
9d		H	CH_3	Cl	83	40	77.82
10a		H	H	H	88	>40	>85.47
10b		CH_3	Ph	H	80	40	71.68
10c		H	CH_3	H	82	2.5	5.18
10d		H	CH_3	Cl	85	26	50.38
11a		H	H	H	78	>40	>73.52
11b		H	CH_3	H	79	>40	>71.68
11c		H	CH_3	Cl	75	35	59.12
Chloroquine	–	–	–	–	–	0.034	0.066

*Isolated yields

of the reaction, the desired product was extracted with ethyl acetate (20 mL × 5 times), and the organic layer was washed with brine solution (30 mL × 4 times) followed by water (20 mL × 5 times). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. Thus, the solid obtained was triturated with chloroform and filtered to afford the title compounds in good to excellent yields.

4-(4-(((2-Oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 6a: Crimson solid. Yield 92%. m.p.245-247°C; IR (KBr) ν_{max}: 3301, 3080, 2926, 2370, 2345, 1701, 1618, 1379, 1342, 1276, 1248, 1192, 1159, 1109, 1046, 941, 842, 774, 755, 619, 550 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, triazole H), 8.17 (d, 2H, *J* = 9.16 Hz, ArH), 8.04 (d, 2H, *J* = 9.16 Hz, ArH), 7.84 (d, 1H, *J* = 8.39 Hz, ArH), 7.67 (t, 1H, *J* = 7.63 Hz, ArH), 7.56 (s, 2H, NH_2), 7.42 (d, 1H, *J* = 8.39 Hz, ArH), 7.35 (t, 1H, *J* = 7.63 Hz, ArH), 6.21 (s, 1H, CH), 5.54 (s, 2H, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.35, 161.58, 152.80, 144.06, 142.67, 138.49, 132.92, 127.55, 124.28, 123.64, 123.08, 120.60, 116.52, 115.05, 91.54, 62.76; HRMS (ESI): Calcd for $C_{18}H_{15}N_4SO_5$: m/z = 399.0800 $[M+H]^+$, found: 399.0759.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(4-(((2-oxo-2*H*-chromen-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 6b**: Light brown solid. Yield 70%. m.p.277-279°C; IR (KBr) ν_{max}: 3432, 3166, 2925, 2370, 1773, 1745, 1611, 1599, 1560, 1508, 1437, 1405, 1358, 1295, 1236, 1165, 1145, 1095, 1054, 875, 835, 787, 747, 608, 577, 459 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H, triazole H), 8.09 (brs, 2H, ArH), 7.98 (brs, 2H, ArH), 7.56 (d, 1H, *J* = 7.79 Hz, ArH), 7.53 (d, 1H, *J* = 7.33 Hz, ArH), 7.31 (d, 1H, *J* = 7.79 Hz, ArH), 7.24 (s, 1H, ArH), 6.95 (d, 1H, *J* = 7.33 Hz, ArH), 6.82 (s, 1H, CH), 5.34 (s, 2H, OCH_2), 1.82 (s, 6H, $2CH_3$); HRMS (ESI): Calcd for $C_{24}H_{21}N_6SO_5$: m/z = 505.1300 $[M+H]^+$, found: 505.1262.

4-((1-(4-(Piperidin-1-ylsulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 6c: Pale yellow solid. Yield 88%. m.p.252-254°C; IR (KBr) ν_{max}: 3088, 2925, 2832, 2371, 2345, 1717, 1621, 1597, 1508, 1451, 1420, 1405, 1375, 1360, 1344, 1310, 1274, 1244, 1194, 1169, 1150, 1140, 1105, 1060, 1025, 980, 935, 885, 843, 754, 707, 602, 583 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.24 (s, 1H, triazole H), 8.23 (d, 2H, *J* = 8.56 Hz, ArH), 7.96 (d, 2H, *J* = 8.56 Hz, ArH), 7.84 (d, 1H, *J* = 7.34 Hz, ArH), 7.67 (t, 1H, *J* = 7.34 Hz, ArH), 7.42 (d, 1H, *J* = 7.34 Hz, ArH), 7.35 (t, 1H, *J* = 7.34 Hz, ArH), 6.20 (s, 1H, CH), 5.55 (s, 2H, OCH_2), 2.95 (t, 4H, *J* = 4.89 Hz, piperidine H), 1.58-1.51 (m, 4H, piperidine H), 1.37 (brs, 2H, piperidine H) ppm; HRMS (ESI): Calcd for $C_{23}H_{23}N_4SO_5$: m/z = 467.1384 $[M+H]^+$, found: 467.1409.

4-((1-(4-(Morpholinosulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 6d: Grey solid. Yield 85%. m.p.210-212°C; IR (KBr) ν_{max}: 3116, 2841, 1707, 1614, 1564, 1504, 1442, 1411, 1354, 1323, 1298, 1244, 1163, 1143, 1101, 1045, 987, 939, 883, 840, 754, 717, 644, 594, 538, 499 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H, triazole H), 8.23 (brs, 2H, ArH), 7.96 (brs, 2H, ArH), 7.57 (brs, 1H, ArH), 7.32 (brs, 1H, ArH), 7.26 (brs, 1H, ArH), 6.95 (brs, 1H, ArH), 6.85 (s, 1H, CH), 5.38 (s, 2H, OCH_2), 3.64 (brs, 4H, morpholine H), 2.93 (brs, 4H, morpholine H); HRMS (ESI): Calcd for $C_{22}H_{21}N_4SO_6$: m/z = 469.1182 $[M+H]^+$, found: 469.1182.

4-((1-(4-((4-(Pyridin-2-yl)piperazin-1-yl)sulfonyl)-phenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy-2*H*-chromen-2-one 6e: Grey solid. Yield 82%; mp: 240-242°C; IR (KBr) ν_{max}: 2848, 1708, 1618, 1591, 1564, 1481, 1436, 1348, 1309, 1273, 1242, 1161, 1110, 1047, 1016, 979, 947, 842, 761, 599, 570 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.20 (brs, 2H, ArH), 8.06 (brs, 1H, pyridyl H), 7.97 (brs, 3H, ArH, pyridyl H), 7.66 (brs, 1H, ArH), 7.50 (brs, 1H, pyridyl H), 7.19 (brs, 1H, ArH), 7.05 (brs, 1H, ArH), 6.80 (brs, 1H, ArH), 6.63 (brs, 1H, pyridyl H), 6.31 (s, 1H, CH), 5.37 (s, 2H, OCH_2), 3.60 (brs, 4H, piperazine H), 3.03 (brs, 4H, piperazine H); HRMS (ESI): Calcd for $C_{27}H_{25}N_6SO_5$: m/z = 545.1607 $[M+H]^+$, found: 545.1611.

4-(4-(((2-Oxo-2*H*-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 7a: Light brown solid. Yield 90%. m.p.228-230°C; IR (KBr) ν_{max}: 3268, 2925, 2369, 2345, 1707, 1609, 1402, 1327, 1280, 1234, 1163, 1131, 1046, 835, 617, 549 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H, triazole H), 8.14 (d, 2H, *J* = 9.16 Hz, ArH), 8.02 (d, 2H, *J* = 9.16 Hz, ArH), 7.66 (d, 2H, *J* = 9.16 Hz, ArH), 7.54 (s, 2H, NH_2), 7.20 (s, 1H, ArH), 7.06 (d, 1H, *J* = 9.16 Hz, CH), 6.31 (d, 1H, *J* = 9.16 Hz, CH), 5.38 (s, 2H, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.00, 160.29, 156.67, 155.32, 144.35, 143.97, 143.52, 129.60, 127.51, 123.47, 120.51, 112.95, 112.85, 101.65, 92.73, 61.54; HRMS (ESI): Calcd for

$C_{18}H_{15}N_4SO_5$: m/z = 399.0800 $[M+H]^+$, found: 399.0764.

4-(4-(((3-Methyl-2-oxo-4-phenyl-2*H*-chromen-7-yl) oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 7b: Off white solid. Yield 82%. m.p.240-242°C; IR (KBr) ν_{max}: 3300, 3216, 3082, 2921, 2369, 1707, 1606, 1369, 1348, 1266, 1179, 1164, 1119, 1072, 1052, 894, 847, 754, 698, 612, 551 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.09 (s, 1H, triazole H), 8.14 (d, 2H, *J* = 8.39 Hz, ArH), 8.02 (d, 2H, *J* = 8.39 Hz, ArH), 7.57 (d, 2H, *J* = 7.63 Hz, ArH), 7.55 (s, 2H, NH_2), 7.53 (s, 1H, ArH), 7.32 (d, 2H, *J* = 7.63 Hz, ArH), 7.26 (d, 1H, *J* = 2.29 Hz, ArH), 6.96 (dd, 1H, ^1J = 9.16 Hz, ^2J = 2.29 Hz, ArH), 6.85 (d, 1H, *J* = 9.16 Hz, ArH), 5.37 (s, 2H, OCH_2), 1.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.60, 160.06, 153.46, 150.22, 143.99, 143.63, 138.54, 134.68, 128.97, 128.77, 128.29, 127.78, 127.59, 123.44, 120.54, 118.83, 114.07, 112.80, 101.65, 61.55, 14.37; HRMS (ESI): Calcd for $C_{25}H_{21}N_4SO_5$: m/z = 489.1220 $[M+H]^+$, found: 489.1230.

4-(4-(((4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy)-methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 7c: Dark brown solid. Yield 88%. m.p.230-232°C; IR (KBr) ν_{max}: 3248, 3189, 3080, 2921, 2367, 1702, 1617, 1596, 1507, 1394, 1334, 1280, 1162, 1097, 1054, 991, 912, 853, 834, 745, 611, 553, 447 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H, triazole H), 8.14 (d, 2H, *J* = 8.56 Hz, ArH), 8.03 (d, 2H, *J* = 8.56 Hz, ArH), 7.71 (d, 1H, *J* = 8.56 Hz, ArH), 7.53 (s, 2H, NH_2), 7.19 (d, 1H, *J* = 2.45 Hz, ArH), 7.08 (dd, 1H, ^1J = 8.56 Hz, ^2J = 2.45 Hz, ArH), 6.23 (s, 1H, CH), 5.39 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.90, 160.11, 154.67, 153.40, 143.97, 143.57, 138.49, 127.52, 126.58, 123.40, 120.47, 113.52, 112.60, 111.40, 101.67, 61.53, 18.15; HRMS (ESI): Calcd for $C_{19}H_{17}N_4SO_5$: m/z = 413.0900 $[M+H]^+$, found: 413.0924.

4-(4-(((6-Chloro-4-methyl-2-oxo-2*H*-chromen-7-yl) oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 7d: Off white solid. Yield 88%. m.p.230-232°C; IR (KBr) ν_{max}: 3421, 2922, 2852, 1701, 1595, 1499, 1412, 1386, 1369, 1342, 1279, 1241, 1207, 1163, 1085, 1066, 1040, 873, 824, 764, 740, 611, 549 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H, triazole H), 8.15 (brs, 2H, ArH), 8.03 (brs, 4H, ArH, NH_2), 7.85 (s, 1H, ArH), 7.51 (s, 1H, ArH), 6.30 (s, 1H, CH), 5.48 (s, 2H, OCH_2), 2.39 (s, 3H, CH_3); HRMS (ESI): Calcd for $C_{19}H_{16}N_4SClO_5$: m/z = 447.0530 $[M+H]^+$, found: 447.0978.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(4-(((2-oxo-2*H*-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 8a**: Light brown solid. Yield 70%. m.p.224-226°C; IR (KBr) ν_{max}: 3448, 3165, 2924, 2345, 1745, 1610, 1599, 1560, 1507, 1437, 1404, 1357, 1294, 1235, 1164, 1145, 1095, 1053, 875, 834, 786, 747, 607, 576, 459 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.08 (s, 1H, triazole H), 8.17 (d, 2H, *J* = 8.39 Hz, ArH), 8.10 (d, 2H, *J* = 8.39 Hz, ArH), 8.00 (d, 1H, *J* = 9.16 Hz, CH), 7.65 (d, 1H, *J* = 9.16 Hz, CH), 7.19 (d, 1H, *J* = 2.29 Hz, ArH), 7.05 (dd, 1H, ^1J = 8.39 Hz, ^2J = 2.29 Hz, ArH), 6.74 (s, 1H, ArH), 6.30 (d, 1H, *J* = 8.39 Hz, ArH), 5.37 (s, 2H, OCH_2), 2.26 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.99, 160.27, 155.85, 155.32, 144.31, 143.52, 129.84, 129.60, 123.43, 119.80, 112.93, 112.82, 112.74, 101.62, 79.30, 78.98, 78.64, 61.53; HRMS (ESI): Calcd for $C_{24}H_{21}N_6SO_5$: m/z 505.1280 $[M+H]^+$. Found: 505.1261.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(4-(((3-methyl-2-oxo-4-phenyl-2*H*-chromen-7-yl)oxy)-methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 8b**: Off white solid. Yield 68%. m.p.258-260°C; IR (KBr) ν_{max}: 3448, 3142, 2924, 2369, 1713, 1598, 1507, 1437, 1400, 1382, 1293, 1264, 1241, 1165, 1146, 1085, 1045, 984, 871, 842, 790, 756, 704, 611, 577 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 1H, triazole H), 8.23 (brs, 2H, ArH), 8.04 (brs, 2H, ArH), 7.57 (d, 2H, *J* = 7.33 Hz, ArH), 7.53 (d, 1H, *J* = 7.33 Hz, ArH), 7.32 (d, 2H, *J* = 7.33 Hz, ArH), 7.25 (s, 1H, ArH), 6.95 (d, 1H, *J* = 7.33 Hz, ArH), 6.84 (d, 1H, *J* = 7.33 Hz, ArH), 6.76 (s, 1H, ArH), 5.35 (s, 2H, OCH_2), 1.98 (s, 3H, CH_3), 1.83 (s, 6H, $2CH_3$); ^{1}HRMS (ESI): Calcd for $C_{31}H_{27}N_6SO_5$: m/z = 595.1758 $[M+H]^+$, found: 595.1726.

***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(4-(((4-methyl-2-oxo-2*H*-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide 8c**: Dark brown solid, yield: 72%. m.p.289-290°C; IR (KBr) ν_{max}: 3511, 3151, 2923, 1718, 1611, 1601, 1425, 1388, 1367, 1280, 1265, 1204, 1162, 1136, 1072, 1044, 991, 844, 786, 746, 627, 609, 577, 562, 453 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, 1H, triazole H), 8.04 (brs, 2H, ArH), 7.90 (brs, 2H, ArH), 7.71 (d, 1H, *J* = 7.79 Hz, ArH), 7.61 (s, 1H, ArH), 7.18 (s, 1H, ArH), 7.08 (brs, 1H, ArH), 6.23 (s, 1H, CH), 5.36 (s, 2H, OCH_2), 2.40 (s, 3H, CH_3), 2.14 (s, 6H, $2CH_3$); HRMS (ESI): Calcd for $C_{25}H_{23}N_6SO_5$: m/z = 519.1445 $[M+H]^+$, found: 519.1434.

4-(4-(((6-Chloro-4-methyl-2-oxo-2H-chromen-7-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide 8d: Dark brown solid. Yield 74%. m.p.232-234°C; IR

(KBr) ν_{max}: 3448, 2923, 2852, 1734, 1602, 1383, 1275, 1142, 1082, 1044, 839, 612, 578 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H, triazole H), 8.11 (brs, 2H, ArH), 8.04 (brs, 2H, ArH), 7.85 (s, 1H, ArH), 7.51 (s, 1H, ArH), 6.58 (s, 1H, ArH), 6.30 (s, 1H, CH), 5.46 (s, 2H, OCH_2), 2.40 (s, 6H, $2CH_3$), 2.21 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.38, 159.75, 158.12, 157.70, 156.69, 155.72, 152.79, 150.45, 150.14, 149.17, 139.06, 129.67, 126.05, 123.58, 113.98, 112.34, 102.22, 82.97, 64.69, 18.16; HRMS (ESI): Calcd for $C_{25}H_{22}N_6SO_5Cl$: m/z = 553.1055 $[M+H]^+$, found: 553.1075.

7-((1-(4-(Piperidin-1-ylsulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 9a: Off white solid. Yield 85%. m.p.221-223°C; IR (KBr) ν_{max}: 3084, 3057, 2937, 2852, 2374, 1727, 1615, 1596, 1505, 1469, 1439, 1400, 1340, 1316, 1281, 1235, 1204, 1160, 1128, 1096, 1042, 1026, 991, 929, 891, 851, 837, 802, 782, 758, 723, 710, 603, 583, 457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H, triazole H), 8.20 (d, 2H, *J* = 8.39 Hz, ArH), 8.01 (s, 1H, *J* = 8.39 Hz, ArH), 7.95 (d, 2H, *J* = 8.39 Hz, ArH), 7.66 (d, 1H, *J* = 8.39 Hz, CH),7.20 (d, 1H, *J* = 2.29 Hz, ArH)**,** 7.06 (dd, 1H, ^1J = 8.39 Hz, ^2J = 2.29 Hz, ArH), 6.31 (d, 1H, *J* = 8.39 Hz, CH), 5.39 (s, 2H, OCH_2), 2.94 (t, 4H, *J* = 5.34 Hz, piperidine H), 1.55 (q, 4H, *J* = 5.34 Hz, piperidine H), 1.39-1.35 (m, 2H, piperidine H) ppm; HRMS (ESI): Calcd for $C_{23}H_{23}N_4SO_5$: m/z = 467.1384 $[M+H]^+$, found: 467.1384.

3-Methyl-4-phenyl-7-((1-(4-(piperidin-1-ylsulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one 9b: Crimson solid. Yield 80%. m.p.215-217°C; IR (KBr) ν_{max}: 2927, 2853, 2371, 1718, 1609, 1507, 1438, 1365, 1342, 1278, 1239, 1173, 1150, 1125, 1094, 1045, 1029, 1015, 934, 824, 759, 720, 703, 604, 583cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.20 (d, 2H, *J* = 8.39 Hz, ArH), 7.94 (d, 2H, *J* = 8.39 Hz, ArH), 7.57 (d, 2H, *J* = 6.87 Hz, ArH), 7.53 (d, 1H, *J* = 6.87 Hz, ArH), 7.32 (d, 2H, *J* = 6.87 Hz, ArH), 7.26 (d, 1H, *J* = 2.29 Hz, ArH), 6.96 (dd, 1H, ^1J = 8.39 Hz, ^2J = 2.29 Hz, ArH), 6.85 (d, 1H, *J* = 8.39 Hz, ArH), 5.38 (s, 2H, OCH_2), 2.93 (t, 4H, *J* = 5.34 Hz, piperidine H), 1.83 (s, 3H, CH_3), 1.54 (q, 4H, *J* = 5.34 Hz, piperidine H), 1.39-1.34 (m, 2H, piperidine H); ^{13}C NMR (100MHz, DMSO-d_6): δ 160.96, 160.20, 155.29, 155.16, 147.01, 144.27, 143.61, 140.51, 139.36, 135.43, 129.57, 129.37, 123.45, 120.64, 118.51, 112.93, 112.81, 112.74, 101.65, 61.50, 46.55, 24.65, 22.76, 14.37; HRMS (ESI): Calcd for $C_{30}H_{29}N_4SO_5$: m/z = 557.1853 $[M+H]^+$, found: 557.1852.

4-Methyl-7-((1-(4-(piperidin-1-ylsulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 9c: White solid. Yield 88%. m.p.235-237°C; IR (KBr) ν_{max}: 2929, 1712, 1604, 1502, 1436, 1363, 1340, 1236, 1168, 1120, 1091, 1014, 935, 827, 756, 702, 599 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.20 (d, 2H, *J* = 8.24 Hz, ArH), 7.95 (d, 2H, *J* = 8.24 Hz, ArH), 7.72 (d, 1H, *J* = 7.79 Hz, ArH), 7.18 (brs, 1H, ArH), 7.08 (d, 1H, *J* = 7.79 Hz, ArH), 6.23 (s, 1H, CH), 5.40 (s, 2H, OCH_2), 2.94 (brs, 4H, piperidine H), 2.40 (s, 3H, CH_3), 1.54 (brs, 4H, piperidine H), 1.36 (brs, 2H, piperidine H); HRMS (ESI): Calcd for $C_{24}H_{25}N_4SO_5$: m/z = 481.1546 $[M+H]^+$, found: 481.1541.

6-Chloro-4-methyl-7-((1-(4-(piperidin-1-ylsulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 9d: Off white solid. Yield 83%. m.p.226-228°C; IR (KBr) ν_{max}: 2939, 2852, 1718, 1608, 1556, 1498, 1446, 1408, 1382, 1340, 1273, 1207,1157, 1089, 1047, 1018, 983, 933, 898, 840, 761, 738, 594 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H, triazole H), 8.20 (d, 2H, *J* = 8.70 Hz, ArH), 7.94 (d, 2H, *J* = 8.70 Hz, ArH), 7.84 (s, 1H, ArH), 7.50 (s, 1H, ArH), 6.30 (s, 1H, CH), 5.49 (s, 2H, OCH_2), 2.94-2.91 (m, 4H, piperidine H), 2.39 (s, 3H, CH_3), 1.57-1.51 (m, 4H, piperidine H), 1.37 (brs, 2H, piperidine H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.80, 155.72, 153.19, 152.86, 143.16, 139.37, 135.48, 129.41, 126.11, 123.76, 120.79, 117.84, 114.04, 112.38, 102.28, 62.46, 46.61, 24.70, 22.83, 18.19; HRMS (ESI): Calcd for $C_{24}H_{24}N_4SO_5Cl$: m/z = 515.1156 $[M+H]^+$, found: 515.1128.

7-((1-(4-(Morpholinosulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 10a: White solid. Yield 88%. m.p.228-232°C; IR (KBr) ν_{max}: 3084, 2921, 2856, 2371, 1726, 1617, 1400, 1349, 1316, 1282, 1261, 1235, 1203, 1176, 1160, 1127, 1112, 1071, 1042, 991, 944, 851, 838, 827, 761, 617, 599, 543, 457 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H, triazole H), 8.23 (d, 2H, *J* = 8.24 Hz, ArH), 8.00 (d, 1H, *J* = 8.70 Hz, CH), 7.96 (d, 2H, *J* = 8.24 Hz, ArH), 7.66 (d, 1H, *J* = 8.70 Hz, CH), 7.20 (d, 1H, *J* = 2.29 Hz, ArH), 7.06 (dd, 1H, ^1J = 8.24 Hz, ^2J = 2.29 Hz, ArH), 6.31 (d, 1H, *J* = 8.24 Hz, ArH), 5.39 (s, 2H, OCH_2), 3.64 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.93 (t, 4H, *J* = 4.58 Hz, morpholine H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.01, 160.28, 155.34, 144.34, 143.71, 139.68, 134.34, 129.68,

129.63, 123.51, 120.80, 112.99, 122.85, 112.75, 101.68, 65.30, 61.53, 45.86; HRMS (ESI): Calcd for $C_{22}H_{21}N_4SO_6$: m/z = 469.1182 $[M+H]^+$, found: 469.1186.

3-Methyl-7-((1-(4-(morpholinosulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4-phenyl-2*H*-chromen-2-one 10b: White solid. Yield 80%. m.p.221-223°C; IR (KBr) ν_{max}: 3120, 2925, 2345, 1708, 1610, 1355, 1299, 1263, 1166, 1146, 1106, 1044, 946, 841, 758, 599, 542 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, triazole H), 8.23 (d, 2H, *J* = 7.79 Hz, ArH), 7.96 (d, 2H, *J* = 7.79 Hz, ArH), 7.57 (d, 2H, *J* = 7.79 Hz, ArH), 7.53 (d, 1H, *J* = 6.41 Hz, ArH), 7.32 (d, 2H, *J* = 7.79 Hz, ArH), 7.26 (s, 1H, ArH), 6.96 (dd, 1H, ^1J = 8.70 Hz, ^2J = 2.29 Hz, ArH), 6.85 (d, 1H, *J* = 8.70 Hz, ArH), 5.38 (s, 2H, OCH_2), 3.64 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.93 (t, 4H, *J* = 4.58 Hz, morpholine H), 1.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.49, 159.95, 153.40, 150.12, 143.68, 139.64, 138.64, 137.62, 134.61, 134.27, 130.61, 129.61, 128.87, 128.68, 128.20, 127.68, 123.42, 120.72, 118.75, 114.00, 112.73, 101.59, 65.24, 61.46, 45.85, 14.32; HRMS (ESI): Calcd for $C_{29}H_{27}N_4SO_6$: m/z = 559.1651 $[M+H]^+$, found: 559.1611.

4-Methyl-7-((1-(4-(morpholinosulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 10c: Grey solid. Yield 82%. m.p.214-216°C; IR (KBr) ν_{max}: 3103, 2923, 2853, 2373, 2345, 1733, 1618, 1596, 1508, 1443, 1386, 1366, 1353, 1310, 1289, 1262, 1201, 1166, 1147, 1118, 1098, 1072, 1049, 1017, 985, 950, 848, 831, 801, 780, 759, 710, 613, 597, 540, 507, 452cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, triazole H), 8.23 (d, 2H, *J* = 8.39 Hz, ArH), 7.96 (d, 2H, *J* = 8.39 Hz, ArH), 7.71 (d, 1H, *J* = 9.16 Hz, ArH), 7.18 (d, 1H, *J* = 2.29 Hz, ArH), 7.08 (dd, 1H, ^1J = 9.16 Hz, ^2J = 2.29 Hz, ArH), 6.23 (s, 1H, CH), 5.40 (s, 2H, OCH_2), 3.64 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.93 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.40 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.88, 160.12, 154.66, 153.40, 143.71, 139.67, 134.32, 129.63, 126.58, 123.48, 120.75, 113.54, 112.63, 111.40, 101.70, 65.28, 61.51, 45.87, 18.14; HRMS (ESI): Calcd for $C_{23}H_{23}N_4SO_6$: m/z = 483.1333 $[M+H]^+$, found: 483.1339.

6-Chloro-4-methyl-7-((1-(4-(morpholinosulfonyl)-phenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one 10d: Light grey solid. Yield 85%. m.p.234-236°C; IR (KBr) ν_{max}: 2974, 1720, 1610, 1556, 1498, 1448, 1408, 1382, 1348, 1303, 1271, 1207, 1161, 1107, 1047, 1018, 985, 943, 898, 842, 765, 740, 715, 596, 543, 501 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.17 (s, 1H, triazole H), 8.24 (d, 2H, *J* = 8.70 Hz, ArH), 7.96 (d, 2H, *J* = 8.70 Hz, ArH), 7.85 (s, 1H, ArH), 7.51 (s, 1H, ArH), 6.30 (s, 1H, CH), 5.49 (s, 2H, OCH_2), 3.64 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.92 (t, 4H, *J* = 4.58 Hz, morpholine H), 2.40 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.83, 155.73, 153.19, 152.87, 143.23, 134.39, 129.71, 126.12, 123.83, 120.87, 117.86, 114.06, 112.41, 102.32, 65.35, 62.44, 45.93, 18.17; HRMS (ESI): Calcd for $C_{23}H_{22}N_4SO_6Cl$: m/z = 517.0949 $[M+H]^+$, found: 517.0928.

7-((1-(4-((4-(Pyridin-2-yl)piperazin-1-yl)sulfonyl)-phenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-2*H*-chromen-2-one 11a: Light grey solid. Yield 78%. m.p.248-250°C; IR (KBr) ν_{max}: 1720, 1481, 1436, 1388, 1346, 1271, 1128, 993, 950, 839, 761, 615, 572 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.21 (brs, 2H, ArH), 8.06 (brs, 1H, pyridyl H), 7.98 (brs, 3H, ArH), 7.65 (brs, 1H, ArH), 7.50 (brs, 1H, ArH), 7.19 (brs, 1H, pyridyl H), 7.06 (brs, 1H, pyridyl H), 6.80 (brs, 1H, pyridyl H), 6.63 (brs, 1H, CH), 6.31 (brs, 1H, CH), 5.37 (s, 2H, OCH_2), 3.60(brs, 4H, piperazine H), 3.03 (brs, 4H, piperazine H); HRMS (ESI): Calcd for $C_{27}H_{25}N_6SO_5$: m/z = 545.1607 $[M+H]^+$, found: 545.1614.

4-Methyl-7-((1-(4-((4-(pyridin-2-yl)piperazin-1-yl)sulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 11b: Grey solid. Yield 79%. m.p.267-269°C; IR (KBr) ν_{max}: 3022, 2360, 1726, 1481, 1436, 1271, 1199, 1130, 950, 839, 761, 613, 572 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H, triazole H), 8.21 (d, 2H, *J* = 8.70 Hz, ArH), 8.06 (d, 1H, *J* = 5.04 Hz, pyridyl H), 7.98 (d, 2H, *J* = 8.70 Hz, ArH), 7.71 (d, 1H, *J* = 8.24 Hz, ArH), 7.50 (brs, 1H, ArH), 7.18 (d, 1H, *J* = 2.29 Hz, ArH), 7.07 (d, 1H, *J* = 7.79, pyridyl H), 6.80 (d, 1H, *J* = 7.79 Hz, pyridyl H), 6.64 (d, 1H, *J* = 5.04 Hz, pyridyl H), 6.23 (s, 1H, CH), 5.38 (s, 2H, OCH_2), 3.61 (brs, 4H, piperazine H), 3.04 (brs, 4H, piperazine H), 2.40 (s, 3H, CH_3); HRMS (ESI): Calcd for $C_{28}H_{27}N_6SO_5$: m/z = 559.1764 $[M+H]^+$, found: 559.1765.

6-Chloro-4-methyl-7-((1-(4-((4-(pyridin-2-yl) piperazin-1-yl)sulfonyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2*H*-chromen-2-one 11c: White solid. Yield 75%. m.p.278-280°C; IR (KBr) ν_{max}: 2841, 1728, 1597, 1498, 1483, 1438, 1409, 1384, 1348,

1313, 1274, 1242, 1209, 1159, 1118, 1089, 1060, 1043, 1020, 985, 948, 887, 837, 765, 738, 597, 567 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.16 (s, 1H, triazole H), 8.22 (d, 2H, *J* = 9.16 Hz, ArH), 8.06 (d, 1H, *J* = 5.50 Hz, pyridyl H), 7.98 (d, 2H, *J* = 9.16 Hz, ArH), 7.84 (s, 1H, ArH), 7.50 (s, 1H, ArH), 6.80 (d, 1H, *J* = 8.70 Hz, pyridyl H), 6.61-6.64 (m, 2H, pyridyl H), 6.29 (s, 1H, CH), 5.47 (s, 2H, OCH_2), 3.59 (t, 4H, *J* = 4.58 Hz, piperazine H), 3.03 (t, 4H, *J* = 4.58 Hz, piperazine H), 2.39 (s, 3H, CH_3); HRMS (ESI): Calcd for $C_{28}H_{26}N_6SO_5Cl$: m/z = 593.1374 $[M+H]^+$, found: 593.1379.

Biological assays

In vitro cultivation of asexual stages of *P. falciparum 3D7*

Cryopreserved 3D7 strain of *P. falciparum* was revived according to standard protocols and introduced into the culture. Asexual erythrocytic stages were cultivated using the procedures of Trager and Jensen with minor modifications[28]. The parasites were cultivated in RPMI-1640 media containing 2 g/L sodium bicarbonate and 40 μg/mL gentamicin sulphate, supplemented with 0.5% AlbuMAX-II. Human erythrocytes at 10% hematocrit were used to culture the parasites, and the cultures were maintained at 37ºC in the presence of a mixture of gasses, 5% CO_2, 5% O_2 and 90% N_2. The level of parasitemia was determined through microscopic examination of Giemsa stained thin blood smears.

Antimalarial activity evaluation

For evaluation of antimalarial activity, [^{3}H]-hypoxanthine incorporation inhibition assay was performed as described elsewhere[9]. The test compounds and chloroquine (positive control) were dissolved in DMSO and double-distilled water, respectively. The working solutions were prepared in RPMI-1640 media and two-fold dilutions were plated in 96-well plates in triplicates (final solvent concentration <0.5%). Separate wells were prepared without the test compounds or chloroquine to monitor uninterrupted growth. Asynchronous *P. falciparum* cultures in 2% parasitemia and 4% final hematocrit were added to each well. After 24 hours of incubation, 20 μL of 0.2 μCi/well [^{3}H] hypoxanthine was added to each well and the plates were incubated for an additional 18 hours. At the end of incubation period, the contents in each well were harvested on a glass-fiber filter mat (Whatman GF/C) using a 96-well semi-automated cell harvester (Skatron). The radioactive associated nucleic acids on the filters were transferred to 5 mL of toluene-based scintillation cocktail and radioactive counts were determined using liquid scintillation beta-counter (Perkin Elmer TriCarb 2900TR). The 50% inhibitory concentration (IC_{50s}) values were determined by plotting the drug concentrations against the percentage viability of the parasites.

Conclusion

A new series of sulfonamide-attached coumarin-[1,2,3]-triazole hybrids was synthesized in good to excellent yields *via* Huisgen 1,3-dipolar cycloaddition reaction of sulfonamide-based azides with various coumarinoalkynes. After spectroscopic characterization, the compounds were evaluated for their *in vitro* antimalarial activity against *P. falciparum* (3D7). Out of the twenty-five synthesized sulfonamide-based coumarin-[1,2,3]-triazole hybrids, four compounds have shown promising antimalarial potency with IC_{50} values <10 μM with a lead molecule **7c** demonstrating an IC_{50} value of 3.64 μM. Collectively, our results indicate that these four lead compounds should be further investigated for their applicability as prototypes for the next generation of sulfonamide-based antimalarials.

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