Med Chem Res (2012) 21:3750–3756
DOI 10.1007/s00044-011-9881-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of some new 4-triazolylmethoxy-2*H*-chromen-2-one derivatives

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Received: 10 August 2011 / Accepted: 4 November 2011 / Published online: 6 December 2011

Abstract 4-(5-Aryl-4*H*-[1,2,4]triazol-3-ylmethoxy)-2*H*-chromen-2-ones have been synthesized by the one pot cyclocondensation reaction of 2-(2-oxo-2*H*-chromen-4-yloxy)acetohydrazide with aromatic/heterocyclic aldehydes in the presence of ammonium acetate in acetic acid. The structures of all the new compounds have been established on the basis of their analytical and spectral data. These compounds were also evaluated for their antibacterial and antifungal activity against various strains of bacteria and fungi and some are found to possess significant antimicrobial activity when compared with ciprofloxacin and miconazole.

Keywords 4-Triazolylmethoxy-2*H*-chromen-2-ones · Cyclocondensation · Antimicrobial activity · Minimum bactericidal concentration · Minimum fungicidal concentration

Introduction

The exploration of heterocycles as privileged structures in drug discovery is, beyond doubt, one of the major areas in medicinal chemistry. These privileged structures represent a class of molecules that act as ligands for various biological receptors with a high degree of binding affinity. These days bacterial infections are becoming more challenging to treat because of the emergence of multi-drug resistant pathogenic bacteria. Therefore, the demand for the discovery of new antimicrobial drug is continually fuelled by the emergence of resistance. Chromen-2-ones have been known to possess various biological activities (Kaswala *et al.*, 2009; Jung *et al.*, 2004; Rehman *et al.*, 2005) such as anticancer, anti-HIV, anticoagulant, antiproliferative, anticonvulsant, and antimicrobial. On the other hand, triazole moiety has also exhibited importance (Ram *et al.*, 1990; Upadhyay *et al.*, 1990; Ergenc *et al.*, 1992; El-Khawass and Habib 1989; Bennur *et al.*, 1976; Zhang *et al.*, 1989) by its presence in a large number of pharmaceuticals. Examples of some antifungal drugs containing 1,2,4-triazole moiety are fluconazole (Tsukuda *et al.*, 1998; Narayanan *et al.*, 1993), itraconazole (Krakovsky and Rybak 1990), ravuconazole (Roberts *et al.*, 2000), and posaconazole (Pfaller *et al.*, 1997). So triazole moiety can be chosen as a possible scaffold as its presence will impact the resulting molecule better activity than the two individual moieties. Keeping this in mind, we have synthesized 4-triazolylmethoxychromen-2-ones and evaluated them for their antibacterial and antifungal activities against three Gram-positive bacteria, two Gram-negative bacteria and four fungi, to find new antimicrobials which are at least as effective as the existing ones. This article reports in detail the synthesis and antimicrobial activity of some new triazolylmethoxy-2*H*-chromen-2-ones.

Results and discussion

Chemistry

The reaction of 4-hyroxychromen-2-one and ethylbromoacetate in the presence of anhydrous K_2CO_3 in dry acetone gave ethyl 2-(2-oxo-2*H*-chromen-4-yloxy)acetate (**2**), which on further treatment with hydrazine hydrate

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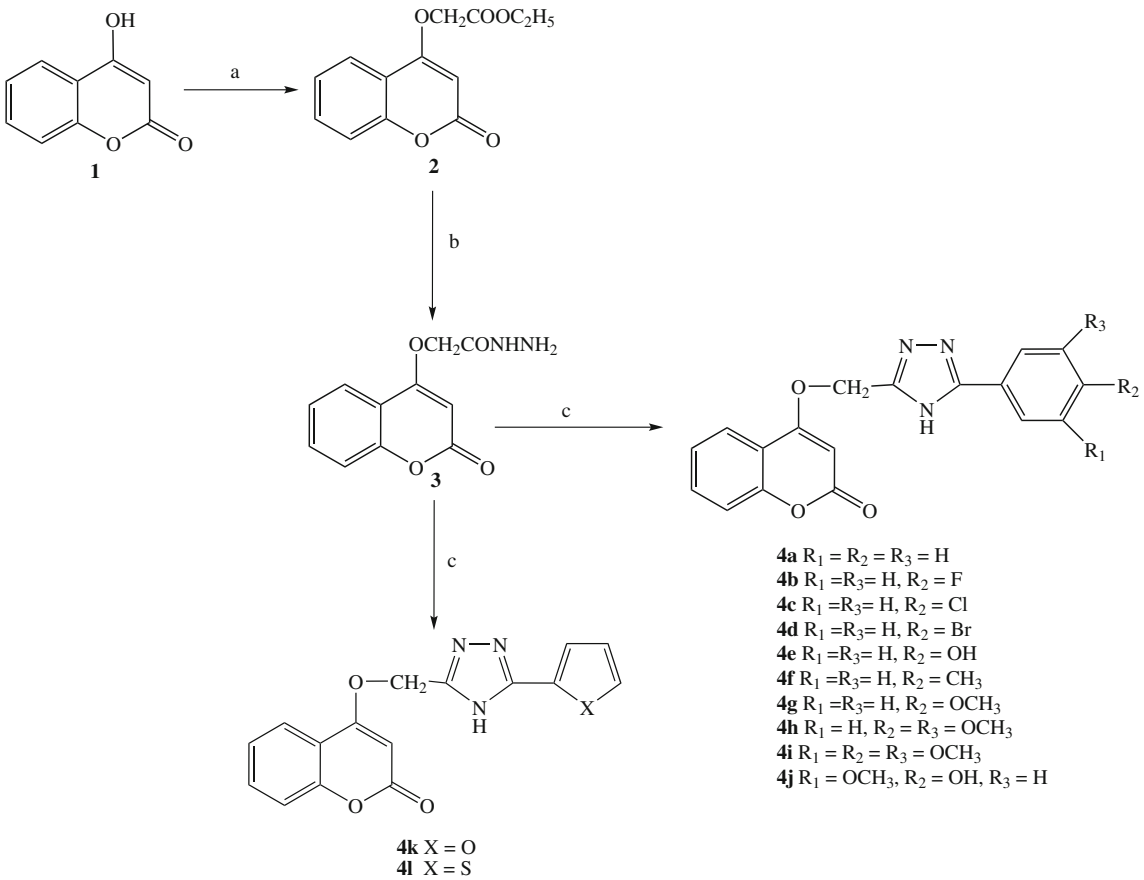
gave 2-(2-oxo-2*H*-chromen-4-yloxy)acetohydrazide (**3**) by following the literature procedure (Chimichi *et al.*, 2002; Abd Elhafez *et al.*, 2003). **3** was cyclocondensed with benzaldehyde in the presence of ammonium acetate in acetic acid to obtain 4-(5-phenyl-4*H*-[1,2,4]triazol-3-yl-methoxy)-2*H*-chromen-2-one (**4a**) (Scheme 1). Its TOF ES + MS showed the M^++1 peak at *m/z* 320.445, corresponding to the molecular formula $C_{18}H_{13}N_3O_3$. Its IR spectrum did not show any absorption band corresponding to $NHNH_2$, as was present in **3** but in addition showed characteristic absorption bands at 1,627 cm^{-1}, thus indicated that cycloaddition has occurred. This was fully supported by its ^1H NMR spectrum, which displayed a characteristic singlet at δ 11.77 integrating for one D_2O exchangeable proton and also a singlet at δ 5.41 (2H) corresponding to $–OCH_2–$. The protons of the phenyl group and aromatic protons of chromen-2-one moiety were observed as singlet and multiplets at δ 7.90 (m, 1H), 7.69 (m, 2H), 7.62 (m, 1H), 7.39 (m, 3H), 7.33 (m, 2H), 5.88 (s, 1H). The ^{13}C NMR spectrum showed all the expected characteristic peaks.

Similar set of above reactions were repeated with substituted aryl/hetero aldehyde to obtain in all 12 corresponding desired compounds.

Biological activity

All the newly synthesized compounds were screened for their in vitro antibacterial and antifungal activity. For antibacterial studies microorganisms employed were *Staphylococcus aureus* (MTCC 096), *Bacillus subtilis* (MTCC 441), *Staphylococcus epidermis* (MTCC 435), *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 424), *Salmonella typhi* (MTCC 733), and *Klebsiella pneumoniae* (MTCC 432). For antifungal screening, *Aspergillus niger* (MTCC 282), *Aspergillus fumigatus* (MTCC 343), *Aspergillus flavus* (MTCC 277), and *Candida albicans* (MTCC 227) strains were used. Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method (Mackie and McCartney 1989) and by measuring zone of inhibition adopting cup-plate method (Chuickshank *et al.*, 1975).



a: $BrCH_2COOC_2H_5$, K_2CO_3, acetone, reflux, 4h; b: $NH_2NH_2.H_2O$, C_2H_5OH, rt, 6h; c: aldehyde, CH_3COONH_4, CH_3COOH, rt, 6-8h

Scheme 1 Synthesis and antimicrobial activity of some new 4-triazolylmethoxy-2*H*-chromen-2-ones

Various concentrations (6.25, 12.5, 25, 50, and 100 μg/ml) of each compound were prepared by serially diluted DMSO from the stock solution. For MIC, a standard drop of the microbial culture, prepared for the assay, was added to the different dilution of compounds in Muller Hilton (MH) broth for bacteria and Sabouraud Dextrose (SD) broth for fungi. Test solutions were then incubated for 16–18 h for bacteria and 28–30 h for fungi at 37°C. MIC is the minimum concentration of the compound, which inhibits the visible growth of bacteria or fungi. To determine zone of inhibition, inoculated MH agar for bacteria and SD agar for fungi were separately poured into the sterilized petri dishes. The poured material was allowed to set and thereafter the "CUPS" (08 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. The test compound solution was added into these cups with the help of a sterile syringe. The plates were incubated at 37°C for 16–18 h for bacteria and 28–30 h for fungi. Clinically antimicrobial drugs Ciprofloxacin and Miconazole were used as the positive control and DMSO was used for blank. The experiments were repeated three times, and the average values are presented in Tables 1 and 2.

Some selected compounds **4b**, **4h–l** were further used for the determination of Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) (Espinel-Ingroff *et. al.*, 2002). The MBC and MFC were determined by incorporating various concentrations of compounds (6.25–100 μg/ml) in MH and SD broth in tubes. One millilitre adjusted spore suspension was added to each tube and incubated at 37°C for 3 days. The MH and SD broths without incorporation of compound and 1 ml of adjusted spore suspension served as a positive control and the broth alone served as a negative control. The tubes which showed no visible growth after 30 h incubation were subcultured on extract-free MHA and SDA plates and incubated at 37°C for 28–30 h. The MBC and MFC were regarded as the minimum concentration of the compound under test, which prevented the growth of any bacterial and fungal colony on the solid medium.

The obtained results, depicted in Tables 1 and 2, revealed that triazolylmethoxy-2*H*-chromen-2-ones **4a–l** could effectively, to some extent, inhibit the growth of all tested strains in vitro. In antibacterial studies, all the compounds tested were less active towards *B. subtilis*, *S. epidermis*, and *P. aeruginosa* as compared to other four strains of bacteria,

Table 2 Antifungal activity data of compounds **4a–l**

Compound	MIC in μg/ml and zone of inhibition[a] (in mm)			
	A. niger	*A. fumigatus*	*A. flavus*	*C. albicans*
4a	12.5 (13–16)	12.5 (11–13)	12.5 (12–15)	6.25 (14–17)
4b	12.5 (13–15)	12.5 (12–14)	12.5 (11–14)	6.25 (14–16)
4c	12.5 (12–14)	25 (<10)	12.5 (12–14)	6.25 (14–16)
4d	12.5 (11–14)	25 (<10)	12.5 (12–14)	6.25 (12–15)
4e	12.5 (12–15)	12.5 (12–14)	25 (<10)	6.25 (15–20)
4f	6.25 (13–15)	25 (11–12)	25 (<10)	6.26 (15–20)
4g	6.25 (12–15)	25 (<10)	25 (<10)	6.25 (14–16)
4h	6.25 (13–16)	25 (<10)	25 (<10)	6.25 (15–20)
4i	6.25 (14–17)	25 (11–13)	25 (<10)	12.5 (12–14)
4j	12.5 (12–14)	12.5 (13–15)	25 (<10)	6.25 (14–16)
4k	6.25 (14–16)	25 (<10)	12.5 (12–14)	6.25 (13–15)
4l	6.25 (15–20)	12.5 (12–15)	12.5 (13–15)	6.25 (15–18)
Miconazole	6.25 (17–22)	12.5 (14–17)	6.25 (17–20)	6.25 (15–20)

[a] Values shown within the parentheses represent zone of inhibition

Table 1 Antibacterial activity data of compounds **4a–l**

Compound	MIC in μg/ml and zone of inhibition[a] (in mm)						
	S. aureus	*B. subtilis*	*S. epidermis*	*E. coli*	*P. aeruginosa*	*S. typhi*	*K. pneumonia*
4a	12.5 (11–14)	12.5 (11–14)	12.5 (12–14)	12.5 (12–14)	12.5 (11–13)	25 (<10)	12.5 (11–14)
4b	6.25 (13–15)	50 (<10)	50 (<10)	12.5 (11–12)	25 (<10)	12.5 (11–14)	6.25 (13–15)
4c	12.5 (12–14)	12.5 (11–13)	50 (<10)	6.25 (13–16)	12.5 (12–15)	12.5 (12–14)	12.5 (12–15)
4d	12.5 (11–14)	12.5 (12–14)	50 (<10)	6.25 (15–18)	25 (<10)	12.5 (11–15)	6.25 (13–17)
4e	12.5 (11–12)	50 (<10)	12.5 (11–12)	6.25 (14–17)	50 (<10)	25 (10)	6.25 (14–16)
4f	12.5 (11–13)	12.5 (11–13)	50 (<10)	12.5 (11–13)	12.5 (11–13)	12.5 (12–14)	12.5 (13–15)
4g	6.25 (13–15)	12.5 (11–13)	25 (<10)	12.5 (11–14)	50 (<10)	25 (<10)	6.25 (14–17)
4h	6.25 (14–16)	25 (<10)	25 (<10)	25 (<10)	25 (<10)	6.25 (13–17)	12.5 (11–14)
4i	6.25 (14-18)	6.25 (14–17)	12.5 (12–14)	12.5 (12–14)	25 (<10)	6.25 (14–18)	12.5 (11–13)
4j	6.25 (15–19)	12.5 (11–13)	50 (<10)	6.25 (13–18)	25 (<10)	6.25 (14–19)	6.25 (15–20)
4k	6.25 (15–18)	50 (<10)	25 (<10)	6.25 (15–20)	12.5 (11–14)	25 (<10)	6.25 (14–18)
4l	6.25 (14–18)	12.5 (11–14)	12.5 (11–13)	6.25 (14–18)	12.5 (12–15)	25 (<10)	6.25 (15–20)
Ciprofloxacin	6.25 (17–22)	6.25 (18–21)	6.25 (15–18)	6.25 (20–24)	6.25 (16–20)	6.25 (19–21)	6.25 (17–20)

[a] Values shown within the parentheses represent zone of inhibition

Table 3 Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) of selected compounds

Compound	MBC in μg/ml			MFC in μg/ml	
	S. aureus	*E. coli*	*K. pneumonia*	*A. niger*	*C. albicans*
4b	12.5	25	25	25	12.5
4h	12.5	25	25	25	25
4i	25	25	25	25	25
4j	12.5	12.5	12.5	12.5	12.5
4k	12.5	12.5	25	12.5	25
4l	6.25	12.5	25	12.5	12.5

where as all the compounds showed moderate to comparable activity against *S. aureus*, *E. coli*, and *K. pneumonia*. Out of four strains of fungi, these triazoles have showed significant activity against *A. niger* and *C. albicans*, where as moderate to mild activity against *A. fumigatus* and *A. flavus*. Compounds **4b**, **4h–l** were selected for MBC and MFC studies against *S. aureus*, *E. coli*, *K. pneumonia*, *A. niger*, and *C. albicans*. The MIC and MBC/MFC of the compounds were not similar, as shown in Table 3. It was observed that the MBC/MFC of the compounds were higher than that of MIC.

Conclusions

Twelve triazolylmethoxy-2*H*-chromen-2-ones were successfully synthesized from 4-hydroxycoumarin in 81–96% yields. The structures of all the compounds were confirmed by their spectral data. All the newly synthesized compounds were screened for their MIC and zone of inhibition against seven strains of bacteria and four strains of fungi. Amongst the compounds screened, some have shown significant antibacterial and antifungal properties, which were further used to determine MBC and MFC against some selected strains of bacteria and fungi. Compounds containing furan and thiophene moiety showed better activity as compared to those containing substituted phenyl group. It is also suggested that triazolylmethoxy-2*H*-chromen-2-ones are worthy for further investigations as potential antimicrobial agent.

Experimental section

Melting points were determined on an electronic apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) and ^{13}C NMR spectra were recorded on Bruker Avance (100 MHz) using tetramethylsilane (TMS) as an internal standard and $CDCl_3$/DMSO-d_6 as solvent. TOF ES + Mass spectra (*m/z*) were recorded on Micromass Autospec LCTKC455. Infrared (FTIR) spectra were determined on a Perkin Elmer-2000 Spectrophotometer instrument. Elemental analyses were performed on a Perkin Elmer series 11, CHNS/O analyzer 2400.

Ethyl 2-(2-oxo-2H-chromen-4-yloxy)acetate (**2**)

4-Hydroxy-2*H*-chromen-2-one (**1**) (5.0 g, 30.86 mmol) was dissolved in 50 ml of dry acetone in a 100 ml round bottom flask. To the mixture, bromoethylacetate (5.15 g, 30.86 mmol) was added along with anhydrous K_2CO_3 (8.0 g). The reaction mixture was refluxed for 6–8 h. After completion of the reaction, the K_2CO_3 was filtered and the filtrate was evaporated under reduced pressure and the residue obtained was subjected to column chromatography. Elutions with 5% ethylacetate:petroleum ether gave **2** as a white solid. Yield 6.9 g (95%); mp 98°C (Lit (Chimichi *et al.*, 2002) mp 97°C); IR ν_{max} 1728, 1716, 1678, 1596, 1475, 1411, 1378, 1274, 1214, 1149, 1014, 995, 779, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, $J = 8.0$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.35 (m, 2H), 5.84 (s, 1H), 4.78 (s, 2H), 4.21 (q, 2H, –$COOCH_2CH_3$), 1.24 (t, $J = 4.8$ Hz, 3H, –$COOCH_2CH_3$).

2-(2-Oxo-2H-chromen-4-yloxy)acetohydrazide (**3**)

A mixture of compound **2** (2.0 g, 8.54 mmol) and hydrazine hydrate (0.51 g, 10.24 mmol) in ethanol was stirred at room temperature for 4 h. The solid that separated out on cooling was filtered and recrystallized from aqueous ethanol to give **3** as white crystalline solid. Yield 1.7 g (90%); mp 192°C; IR ν_{max} 3302, 1720, 1686, 1623, 1521, 1413, 1356, 1276, 1207, 1113, 1033, 999, 946, 882, 849, 758, 582 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.56 (s, 1H, D_2O exchangeable), 8.03 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.34 (m, 2H), 5.82 (s, 1H), 4.76 (s, 2H), 4.38 (brs, 2H, D_2O exchangeable); TOF ES + MS *m/z*: 235.449.

General procedure

Synthesis of 4-(5-aryl-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one

2-(2-Oxo-2*H*-chromen-4-yloxy)acetohydrazide (**3**) (0.20 g, 0.85 mmol) and benzaldehyde (0.091 g, 0.85 mmol) was dissolved in 10 ml of glacial acetic acid in a 50-ml round bottom flask. To the mixture, ammonium acetate was added and then stirred for 6 h at room temperature. The progress of the reaction was monitored by TLC. After the

completion of the reaction, the reaction mixture was poured into ice cold water and neutralize with ammonia. The precipitated product was filtered, washed with water, and crystallized from chloroform/methanol to give the desired product.

*4-(5-Phenyl-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4a**)*

Yield 90%; mp 226°C; IR ν_{max} 3448, 2924, 1721, 1690, 1627, 1451, 1399, 1274, 1224, 1191, 1160, 1142, 1117, 941, 887, 825, 754, 690, 567 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.77 (s, 1H, >NH, D_2O exchangeable), 7.90 (m, 1H), 7.69 (m, 2H), 7.62 (m, 1H), 7.39 (m, 3H), 7.33 (m, 2H), 5.88 (s, 1H), 5.41 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.4, 161.9, 153.2, 144.7, 134.2, 130.3, 129.0, 127.4, 124.5, 116.7, 115.7, 91.6, 66.4 (–OCH_2–); TOF ES + MS *m/z* 320.445; Anal. Calcd. for $C_{18}H_{13}N_3O_3$, Calculated: C 67.71%, H 4.10%, N 13.16%, Found: C 67.33%, H 4.11%, N 13.21%.

*4-(5-(4-Fluorophenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4b**)*

Yield 94%; mp 244°C; IR ν_{max} 3448, 2970, 1715, 1683, 1628, 1500, 1433, 1402, 1310, 1276, 1256, 1231, 1159, 1118, 949, 867, 831, 762, 672, 521 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.75 (s, 1H, > NH, D_2O exchangeable), 7.91 (m, 1H), 7.87 (d, $J = 7.6$ Hz, 2H), 7.72 (m, 1H), 7.51 (m, 1H), 7.32 (d, $J = 7.6$ Hz, 2H), 7.24 (m, 1H), 5.76 (s, 1H), 5.28 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.8, 164.8, 153.1, 149.2, 144.3, 133.9, 131.7, 125.2, 124.4, 122.5, 116.7, 110.4, 108.6, 92.4, 67.3 (–OCH_2–); TOF ES + MS *m/z* 338.449; Anal. Calcd. for $C_{18}H_{12}FN_3O_3$, Calculated: C 64.09%, H 3.59%, N 12.46%, Found: C 64.01%, H 3.44%, N 12.53%.

*4-(5-(4-Chlorophenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4c**)*

Yield 92%; mp 205°C; IR ν_{max} 3448, 2965, 1723, 1697, 1626, 1569, 1493, 1441, 1311, 1273, 1253, 1195, 1141, 1067, 938, 859, 815, 765, 710 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.74 (s, 1H, > NH, D_2O exchangeable), 7.91 (m, 1H), 7.88 (d, $J = 7.8$ Hz, 2H), 7.70 (m, 1H), 7.55 (m, 1H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.24 (m, 1H), 5.71 (s, 1H), 5.26 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.4, 164.1, 153.3, 148.9, 146.4, 135.9, 131.7, 125.2, 123.0, 122.5, 115.4, 110.4, 109.5, 92.6, 67.6 (–OCH_2–); TOF ES + MS *m/z* 354.886; Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$, Calculated: C 61.11%, H 3.42%, N 11.88%, Found: C 61.23%, H 3.51%, N 11.79%.

*4-(5-(4-Bromophenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4d**)*

Yield 91%; mp 249°C; IR ν_{max} 3212, 2926, 1686, 1611, 1581, 1457, 1375, 1254, 1160, 1141, 1112, 951, 818, 751 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.71 (s, 1H, >NH, D_2O exchangeable), 7.94 (m, 1H), 7.54 (m, 1H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.24 (m, 2H), 6.82 (d, $J = 7.6$ Hz, 2H), 5.75 (s, 1H), 5.26 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.4, 162.4, 153.2, 149.0, 144.1, 136.5, 127.0, 124.7, 121.8, 116.4, 110.1, 109.3, 91.4, 66.4 (–OCH_2–). TOF ES + MS *m/z* 399.398; Anal. Calcd. for $C_{18}H_{12}BrN_3O_3$, Calculated: C 54.29%, H 3.04%, N 10.55%, Found: C 54.33%, H 3.01%, N 10.67%.

*4-(5-(4-Hydroxyphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4e**)*

Yield 94%; mp 219°C; IR ν_{max} 3198, 2929, 1689, 1670, 1609, 1438, 1405, 1361, 1253, 1192, 1164, 1114, 954, 828, 765 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.45 (s, 1H, >NH, D_2O exchangeable), 9.74 (brs, 1H, –OH, D_2O exchangeable), 7.92 (m, 1H), 7.51 (m, 1H), 7.42 (d, $J = 7.8$ Hz, 2H), 7.23 (m, 2H), 6.75 (d, $J = 7.8$ Hz, 2H), 5.58 (s, 1H), 5.24 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1, 164.7, 153.0, 146.5, 144.3, 132.9, 131.7, 126.1, 124.4, 123.0, 114.6, 110.7, 108.4, 92.6, 67.1 (-OCH_2-); TOF ES + MS *m/z* 336.561; Anal. Calcd. for $C_{18}H_{13}N_3O_4$, Calculated: C 64.48%, H 3.91%, N 12.53%, Found: C 64.50%, H 3.86%, N 12.61%.

*4-(5-(4-Methylphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4f**)*

Yield 90%, mp 144°C; IR ν_{max} 3213, 2924, 1686, 1609, 1457, 1399, 1254, 1160, 1144, 1115, 944, 818, 752 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.87 (s, 1H, >NH, D_2O exchangeable), 7.99 (m, 1H), 7.88 (m, 1H), 7.61 (m, 2H), 7.37 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 7.8$ Hz, 2H), 5.86 (s, 1H), 5.44 (s, 2H, –OCH_2–), 2.33 (s, 3H, -CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.5, 155.3, 148.1, 142.3, 136.4, 132.9, 130.6, 128.5, 126.6, 125.7, 124.3, 117.4, 94.7, 92.5, 68.5 (–OCH_2–), 22.6 (–CH_3); TOF ES + MS *m/z* 334.554; Anal. Calcd. for $C_{19}H_{15}N_3O_3$, Calculated: C 68.46%, H 4.54%, N 12.61%, Found: C 68.39%, H 4.66%, N 12.70%.

*4-(5-(4-Methoxyphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4g**)*

Yield 96%; mp 180°C; IR ν_{max} 3422, 2967, 1719, 1681, 1625, 1399, 1308, 1252, 1232, 1117, 946, 832, 754 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 11.64 (s, 1H, >NH, D_2O exchangeable), 7.97 (m, 1H), 7.71 (m, 1H), 7.67 (m, 2H),

7.38 (d, $J = 8.0$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 5.88 (s, 1H), 5.44 (s, 2H, –OCH_2–), 3.80 (s, 3H, –OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 169.4, 167.2, 151.7, 149.6, 147.7, 142.6, 134.3, 130.1, 128.9, 126.6, 125.7, 124.4, 115.7, 94.8, 92.6, 68.5 (–OCH_2–), 56.8 (-OCH_3); TOF ES + MS *m/z* 350.672; Anal. Calcd. for $C_{19}H_{15}N_3O_4$, Calculated: C 65.32%, H 4.33%, N 12.03%, Found: C 65.41%, H 4.29%, N 12.11%.

*4-(5-(3,4-Dimethoxyphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4h**)*

Yield 95%; mp 196°C; IR ν_{max} 3436, 2928, 1718, 1684, 1627, 1508, 1420, 1306, 1268, 1188, 1140, 1114, 932, 758 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.63 (s, 1H, >NH, D_2O exchangeable), 7.93 (m, 1H), 7.66 (m, 1H), 7.36 (m, 2H), 7.31 (s, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 6.99 (d, $J = 7.6$ Hz, 1H), 5.83 (s, 1H), 5.45 (s, 2H, –OCH_2–), 3.81 (s, 6H, 2 x –OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.4, 165.2, 153.2, 144.8, 133.3, 127.1, 124.7, 121.9, 116.9, 111.9, 108.9, 91.6, 66.5 (–OCH_2–), 55.9 (–OCH_3); TOF ES + MS *m/z* 380.447; Anal. Calcd. for $C_{20}H_{17}N_3O_5$, Calculated: C 63.32%, H 4.52%, N 11.08%, Found: C 63.41%, H 4.60%, N 11.04%.

*4-(5-(3,4,5-Trimethoxyphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4i**)*

Yield 96%; mp 192°C; IR ν_{max} 3420, 2941, 1718, 1684, 1621, 1505, 1417, 1329, 1248, 1196, 1128, 951, 829, 769 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.74 (s, 1H, >NH, D_2O exchangeable), 7.92 (m, 1H), 7.86 (s, 2H), 7.54 (m, 1H), 7.28 (m, 2H), 5.64 (s, 1H), 5.34 (s, 2H, –OCH_2–), 3.80 (s, 6H, 2 x -OCH_3), 3.71 (s, 3H, –OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.1, 162.1, 153.2, 145.0, 139.5, 129.5, 124.2, 116.5, 104.7, 91.3, 66.2(–OCH_2–), 60.6 (–OCH_3–), 56.1 (–OCH_3), 55.8 (–OCH_3); TOF ES + MS *m/z* 410.671; Anal. Calcd. for $C_{21}H_{19}N_3O_6$, Calculated: C 61.61%, H 4.68%, N 10.26%, Found: C 61.50%, H 4.65%, N 10.18%.

*4-(5-(4-Hydroxy-3-methoxyphenyl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4j**)*

Yield 91%; mp 210°C; IR ν_{max} 3199, 2930, 1686, 1609, 1508, 1401, 1318, 1289, 1187, 1113, 946, 820, 765 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.67 (s, 1H, >NH, D_2O exchangeable), 7.92 (m, 1H), 7.61 (m, 1H), 7.36 (m, 2H), 7.27 (s, 1H), 7.06 (d, $J = 7.8$ Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 5.76 (s, 1H), 5.40 (s, 2H, –OCH_2–), 3.86 (s, 3H, –OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.8, 161.8, 153.1, 146.4, 144.3, 133.9, 131.7, 125.5, 122.3, 116.7, 114.6, 110.7, 108.6, 92.6, 92.4, 67.3 (–OCH_2–), 54.9 (–OCH_3); TOF ES + MS *m/z* 366.498; Anal. Calcd. for $C_{19}H_{15}N_3O_5$, Calculated: C 62.46%, H 4.14%, N 11.50%, Found: C 62.49%, H 4.09%, N 11.67%.

*4-(5-(Furan-2-yl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4k**)*

Yield 83%; mp 190°C; IR ν_{max} 3432, 2924, 1727, 1686, 1629, 1570, 1411, 1398, 1300, 1225, 1184, 1116, 930, 830, 747 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.75 (s, 1H, >NH, D_2O exchangeable), 7.91 (m, 2H), 7.70 (m, 1H), 7.63 (m, 1H), 7.35 (m, 1H), 6.83 (m, 1H), 6.55 (m, 1H), 5.73 (s, 1H), 5.34 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.9, 164.7, 152.8, 149.0, 138.0, 134.5, 124.2, 123.0, 116.4, 113.9, 112.2, 91.2, 65.9 (–OCH_2–). TOF ES + MS *m/z* 310.430; Anal. Calcd. for $C_{16}H_{11}N_3O_4$, Calculated: C 62.14%, H 3.58%, N 13.59%, Found: C 61.91%, H 3.41%, N 13.44%.

*4-(5-(Thiophen-2-yl)-4H-[1,2,4]triazol-3-ylmethoxy)-2H-chromen-2-one (**4l**)*

Yield 81%; mp 201°C; IR ν_{max} 3431, 2929, 1727, 1684, 1620, 1585, 1475, 1394, 1316, 1275, 1184, 1112, 951, 836, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.78 (s, 1H, >NH, D_2O exchangeable), 7.92 (m, 2H), 7.70 (m, 1H), 7.65 (m, 1H), 7.35 (m, 1H), 6.88 (m, 1H), 6.57 (m, 1H), 5.71 (s, 1H), 5.33 (s, 2H, –OCH_2–); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.9, 164.7, 152.8, 149.0, 138.0, 134.5, 132.8, 124.2, 116.4, 113.9, 112.2, 91.2, 65.9 (-OCH_2-); TOF ES + MS *m/z* 326.603; Anal. Calcd. for $C_{16}H_{11}N_3O_3S$, Calculated: C 59.07%, H 3.41%, N 12.92%, Found: C 59.19%, H 3.24%, N 13.08%.

Acknowledgments Siva S. Panda and Mahesh Chand are thankful to UGC (New Delhi) for financial assistance.

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