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Short Communication

One Pot Synthesis and Characterization of 1,2,3-Triazole Xanthenones As Potent Anti-Bacterial Agents

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ABSTRACT

*A series of 12-[4-(1-Phenyl-1H-[1,2,3]-triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo [a] xanthen-11-one derivatives **(IVa-j)** have been synthesized via one-pot three component reaction of 2-naphthol, substituted 4-(1-Phenyl-1H-[1,2,3]-triazol-4-ylmethoxy)-benzaldehydes and cyclic 1,3-diketones in the presence of catalytic amount of iodine gave excellent yields. The newly synthesized compounds were characterized by analytical and spectral data. All the compounds were screened for their antibacterial activity.*

Keywords: Iodine, Xanthenones, 2-Naphthol, Dimedones.

INTRODUCTION

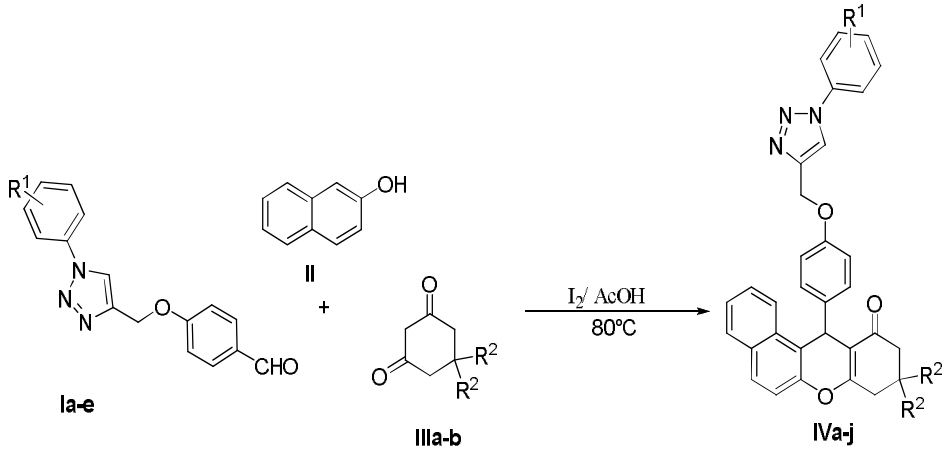
Design of highly efficient chemical reaction sequences that provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties is a major challenge of modern drug discovery [1]. Recently, multi-component reactions have emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economy and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described advantages of multi-component reactions [2-4]. Thus, they are perfectly amenable to automation for combinatorial synthesis [5]. Xanthenes and benzoxanthenes have drawn much attention in the field of medicinal chemistry. These have been reported to exhibit various biological and therapeutic properties such as antiproliferative, antineoplastic [6], analgesic, anti-inflammatory [7], antibacterial [8], antiviral [9], antimalarial [10], and antitumor activities [11]. These are being utilized as antagonists for paralyzing action of Zoxazolamine. Besides, these heterocyclic molecules have been widely used as dyes, P^H-sensitive fluorescent materials for visualization of biomolecules and also found in laser technologies. 1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications as pharmaceutical agents. Perusal of literature triazoles act as antifungal [12], antibacterial [13-15], antiallergic [16], antiplatelet [17], anti-HIV [18,19], anti-inflammatory [20], anticonvulsant [21], β-lactamase inhibitors [22], antiviral[23], and antitubercular agents [24,25]. The present paper reports the synthesis, characterization and biological activity of 1,2,3 triazole Xanthenone derivatives.

MATERIALS AND METHODS

Melting points were determined in open glass capillary tube on a Gallen-Kamp MFB-595 apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR-8400s, using samples in KBr disks. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 spectrometer using $CDCl_3$ as solvent and TMS as the internal standard, the chemical shifts are expressed in δ ppm. Mass spectra were recorded on SHIMADZU LCMS 2020 Massspectrometer. The progress of reactions was monitored by TLC (Silica gel, aluminium sheets 60 F_{254}, Merck). Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer.

A mixture of substituted 4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-benzaldehydes **Ia-e** (1 mmol), β-naphthol **II** (1 mmol), substituted dimedones **IIIa,b** (1.2 mmol) and I_2 (0.1 mmol) in acetic acid was heated at the 80°C for 1-2h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, treated with aqueous $Na_2S_2O_3$, then extracted with ethyl acetate and evaporated the solvent under reduced pressure. The products were obtained in good yields (75-80%). The crude products were purified by silica-gel column chromatography using ethyl acetate–hexane as eluent.

Scheme 1:



Scheme 2: R^1 = H, 2-Cl, 4-Cl, 2-OMe, 4-OH; R^2= CH_3, H.

RESULTS AND DISCUSSION

A mixture of 2-naphthol **(II)** (1 mmol), 4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-benzaldehyde **(Ia)** (1 mmol) and 1,3-diketone **(III)** (1.2 mmol) in the presence of iodine in acetic acid yielded 12-[4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one **(IVa)**. The newly synthesized compound was characterized by ^{1}H NMR, ^{13}C NMR and Mass spectral data. In the ^{1}H NMR spectrum of compound **IVa,** the characteristic singlet for C-H proton appeared at δ 6.01 and 6 C-H protons appeared at δ 2.01-2.83 as multiplet. In the ^{13}C-NMR spectrum, the carbonyl carbon appeared at 197.1 ppm. The LCMS spectrum exhibited the $[M+H]^+$ peak at m/z 500. Thus, on the basis of above studies **IVa** has been assigned structure 12-[4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one.

Spectral data

IVa:12-[4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one: Yield 80%,mp: 185-187^{o}C.IR (KBr): 1647, 1596, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01-2.13 (m, 2H), 2.51-2.54 (m, 2H), 2.71-2.83 (m, 2H), 5.62 (s, 2H, OCH_2), 6.01 (s, 1H, CH), 7.41-7.45 (m, 8H), 7.63-7.67 (m, 4H), 7.81-7.85 (m, 2H), 8.01 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 20.7, 28.1, 39.8, 59.8, 111.4, 115.4, 116.4, 119.5, 121.4, 122.5, 122.7, 122.8, 122.9, 123.0, 123.4, 124.9, 125.1, 127.6, 129.0, 131.1, 134.1, 147.8, 150.6,165.7, 197.1;MS (m/z): 500 $[M+H]^+$; Anal. Calc. for $C_{32}H_{25}N_3O_3$: C, 76.94; H, 5.04; N, 8.41. Found: C, 76.58; H, 4.98; N, 8.35.

IVb:12-{4-[1-(2-Chloro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-8,9,10,12-tetrahydro-benzo [a]xanthen-11-one: Yield 78%,mp: 190-192^{o}C.IR (KBr): 1638, 1595, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12-2.25 (m, 2H), 2.50-2.58 (m, 2H), 2.80-2.89 (m, 2H), 5.99 (s, 2H, OCH_2), 5.99 (s, 1H, CH), 7.19-7.59 (m, 11H), 7.80 (m, 2H), 8.01 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 20.7, 27.5, 42.5, 62.3, 110.8, 115.2, 116.5, 119.4, 121.4, 122.8, 122.9, 123.2, 123.3, 123.5, 123.8, 123.9, 124.3, 125.1, 127.5, 129.1, 131.1, 134.1, 147.7, 150.9, 165.5, 197.2;MS (m/z): 534$[M+1]^+$; Anal. Calc. for $C_{32}H_{24}ClN_3O_3$: C, 71.97; H, 4.53; Cl, 6.64; N, 7.87. Found: C, 71.68; H, 4.48; N, 7.80.

IVc:12-{4-[1-(4-Chloro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-8,9,10,12-tetrahydro-benzo [a]xanthen-11-one: Yield 74%,mp: 185-187^{o}C.IR (KBr): 1638, 1595, 1506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25-2.32 (m, 2H), 2.65-2.82 (m, 2H), 2.82-2.89 (m, 2H), 4.91 (s, 2H, OCH_2), 6.02 (s, 1H, CH), 7.45-7.50 (m, 6H), 7.65-7.71 (m, 4H), 7.91-7.95 (m, 4H), 7.99 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 20.3, 27.5, 36.9, 59.9, 112.0, 115.1, 117.3, 119.2, 121.4, 123.0, 123.5, 123.6, 124.5, 124.9, 127.0, 128.6, 129.2, 129.7, 131.2, 131.4, 134.0, 147.8, 150.5, 167.0, 197.0;MS (m/z): 534$[M+1]^+$; Anal. Calc. for $C_{32}H_{24}ClN_3O_3$: C, 71.97; H, 4.53; Cl, 6.64; N, 7.87. Found: C, 71.68; H, 4.48; N, 7.80.

VId:12-{4-[1-(2-Methoxy-phenyl)-1H-[1,2,3]triazol-4-ylmethoxy]-phenyl}-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one: Yield 79%,mp: 200-202^{o}C.IR (KBr): 1636, 1587, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09-2.14 (m, 2H), 2.36-2.42 (m, 2H), 2.62-2.75 (m, 2H), 3.89 (s, 3H, -OCH_3), 5.39 (s, 2H, OCH_2), 5.98 (s, 1H, CH), 6.98-7.00 (m, 2H), 7.29-7.45 (m, 8H), 7.69-7.81 (m, 3H), 8.08 (d,1H), 8.19 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.5, 27.5, 37.0, 50.9, 65.5, 110.8, 114.4, 116.4, 118.9, 121.4, 121.8, 122.9, 123.2, 123.5, 123.6, 123.8, 123.9, 124.3, 124.9, 125.2, 127.6, 129.1, 129.5, 131.5, 134.0, 147.4, 150.8, 165.6 197.1;MS (m/z): 530$[M+H]^+$; Anal. Calc. for $C_{33}H_{27}N_3O_4$: C, 74.84; H, 5.14; N, 7.93. Found: C, 74.69; H, 5.05; N, 7.85.

IVe:12-{4-[1-(4-Hydroxy-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-8,9,10,12-tetrahydro-benzo [a]xanthen-11-one: Yield 73%,mp: 158-160^{o}C.IR: 1635, 1591, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06-2.12 (m, 2H), 2.38-2.43 (m, 2H), 2.70-2.75 (m, 2H), 5.26 (s, 2H, OCH_2), 5.80 (s, 1H, CH), 7.40- 7.52 (m, 7H), 7.90-7.95 (m, 4H), 8.30 (d, 2H), 8.52 (s, 1H), 9.95 (s, 1H, -OH);^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.5, 27.8, 39.4, 61.9, 119.7, 115.1, 117.4, 119.6, 121.5, 123.0, 123.5, 123.8, 124.9, 128.5, 129.2, 129.6, 131.2, 131.4, 134.5, 147.8, 151.2, 167.5, 197.3; MS (m/z): 516$[M+H]^+$; Anal. Calc. for $C_{32}H_{25}N_3O_4$: C, 74.55; H, 4.89; N, 8.15. Found: C, 74.36; H, 4.75; N, 8.05.

IVf:9,9-Dimethyl-12-[4-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo [a]xanthen-11-one: Yield 76%,mp: 193-195^{o}C.IR (KBr):1630, 1615, 1560cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H), 1.15 (s, 3H), 2.35-2.34 (m, 2H), 2.69-2.74 (m, 2H), 5.52 (s, 2H, OCH_2), 6.02 (s, 1H, CH), 7.40-7.65 (m, 6H), 7.65-7.69 (m, 4H), 7.80-7.88 (m, 4H), 8.01-8.06 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 27.5, 29.0, 32.4, 41.4, 50.8, 62.5, 117.4, 119.2, 120.3, 123.0, 123.5, 123.8, 124.9, 127.0, 128.6, 129.0, 129.2, 129.5, 131.4, 147.8, 190.5;MS (m/z): 528$[M+H]^+$;Anal. Calcd for $C_{34}H_{29}N_3O_3$: C, 77.40; H, 5.54; N, 7.96. Found: C, 77.32; H, 5.40; N, 7.89.

IVg:12-{4-[1-(2-Chloro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-9,9-dimethyl-8,9,10,12-tetra hydro-benzo[a]xanthen-11-one: Yield 78%,mp: 187-189^{o}C.IR (KBr):1632, 1619, 1566 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 3H), 1.18 (s, 3H), 2.25-2.35 (m, 2H), 2.58-2.67 (m 2H), 5.42 (s, 2H, O-CH_2), 6.01 (s, 1H, CH), 7.29-7.42 (m, 7H), 7.51-7.59 (m, 4H), 7.78-7.82 (m, 2H), 8.01 (s, 1H), 8.08 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 27.2, 29.3, 32.4, 51.8, 60.5, 111.2, 115.1, 117.3, 119.2, 121.4, 123.2, 123.5, 125.1, 128.5, 129.1, 129.5, 131.1, 131.5, 131.7, 132.6, 134.1, 136.1, 138.0, 147.5, 150.5, 165.5, 196.0;MS (m/z): 562[M+H]$^{+}$; Anal. Calc. for $C_{34}H_{28}ClN_3O_3$: C, 72.66; H, 5.02; Cl, 6.31; N, 7.48. Found: C, 71.60; H, 4.99; N, 7.39.

IVh:12-{4-[1-(4-Chloro-phenyl)-1H-[1,2,3]triazol-4-ylmethoxy]-phenyl}-9,9-dimethyl-8,9,10,12-tetra hydro-benzo[a]xanthen-11-one: Yield 80%,mp: 183-185^{o}C.IR (KBr):1635, 1622, 1565 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.15 (s, 3H), 2.21-2.36 (m, 2H), 2.59-2.70 (m, 2H), 5.02 (s, 2H, OCH_2), 5.98 (s, 1H, CH), 7.31-7.48 (m, 6H), 7.59-7.75 (m, 2H), 7.79-7.89 (m, 2H), 7.99 (s, 1H), 8.05 (m,1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 27.4, 29.0, 32.4, 41.4, 50.8, 62.9, 111.4, 115.1, 117.4, 119.0, 121.4, 123.0, 123.2, 123.5, 124.9, 127.1, 128.6, 128.9, 129.1, 129.7, 131.1, 131.4, 134.0, 147.8, 150.5, 165.9, 197.0;MS (m/z): 562[M+H]$^{+}$; Anal. Calc. for $C_{34}H_{28}ClN_3O_3$: C, 72.66; H, 5.02; Cl, 6.31; N, 7.48. Found: C, 71.60; H, 4.99; N, 7.39.

IVi:12-{4-[1-(2-Methoxy-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-9,9-dimethyl-8,9,10,12-tetra hydro-benzo[a]xanthen-11-one: Yield 79%,mp: 143-145^{o}C.IR (KBr):1639, 1616, 1561 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08. (s, 3H), 1.12 (s, 3H), 1.93-2.22 (m, 2H), 2.68-2.75 (m, 2H), 3.80 (s, 3H, OCH_3), 5.19 (s, 2H, OCH_2), 5.82 (s, 1H, CH), 7.02-7.05 (m, 2H), 7.21-7.25 (m, 1H), 7.34-7.45 (m, 4H), 7.52-7.59 (m, 1H), 7.85-7.89 (m, 4H), 8.32 (d, 1H), 8.39 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$):δ 25.5, 26.2, 28.5, 32.0, 50.0, 56.0, 63.5, 110.5, 112.9, 115.8, 117.2, 120.8, 123.3, 123.8, 123.9, 125.0, 125.5, 127.1, 127.2, 128.4, 129.0, 130.3, 130.5, 130.8, 147.0, 149.1, 150.8, 165.1, 196.2;MS (m/z): 558[M+H]$^{+}$; Anal. Calc. for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54. Found: C, 75.20; H, 5.51; N, 7.42.

IVj:12-{4-[1-(4-Hydroxy-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-phenyl}-9,9-dimethyl-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one: Yield 75%,mp: 140-142^{o}C.IR (KBr):1635, 1617, 1568 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05. (s, 3H), 1.11 (s, 3H), 2.20-2.26 (m, 2H), 2.62-2.73 (m, 2H), 5.19 (s, 2H, OCH_2), 5.79 (s, 1H, CH), 6.78-6.80 (m, 4H), 7.39-7.57 (m, 5H), 7.85 (m, 4H), 8.25 (d, 1H), 8.69 (s, 1H), 9.91 (s, 1H, -OH);^{13}C NMR (100 MHz, $CDCl_3$):δ 25.5, 26.5, 28.7, 32.1, 50.0, 62.5, 110.7, 115.6, 115.9, 117.1, 120.0, 121.2, 121.4, 123.1, 123.5, 125.0, 127.1, 128.5, 128.6, 129.0, 129.2, 130.5, 130.8, 131.2, 147.0, 150.2, 157.3, 165.5, 196.1;MS (m/z): 544 [M+H]$^{+}$; Anal. Calc. for $C_{34}H_{29}N_3O_4$: C, 75.12; H, 5.38; N, 7.73. Found: C, 75.01; H, 5.25; N, 8.62.

Biological Assay

Antibacterial Activity: All the synthesized compounds were screened *in vitro* for their antibacterial activity against two gram +ve bacterial strains *Staphylococcus aureus* (ATCC-9144), *Bacillus cereus* (ATCC-11778) and two gram –ve bacterial strains *Escherichia coli* (ATCC-8739), *Proteus vulgaris* (ATCC-29213) were used to determine by the cup-plate agar diffusion method at 25µg mL^{-1}, 50µg mL^{-1} and 100µg mL^{-1} concentrations. These experiments carried out by three times. The zone of inhibition (in mm) was compared with standard drug Ampicillin and the results are tabulated in table 1. All the newly synthesized compounds were active against all the tested strains.

Table 1. Antibacterial activity of the synthesized compounds **IVa-j**.

Product	Zone of inhibition in mm											
	S. aureus (ATCC-9144)			*B. cereus* (ATCC-11778)			*E. coli* (ATCC-8739)			*P. vulgaris* (ATCC- 29213)		
	25	50	100	25	50	100	25	50	100	25	50	100
IVa	08	10	10	11	13	15	12	13	15	10	12	13
IVb	05	05	06	04	04	06	10	10	14	07	08	10
IVc	05	06	07	04	05	06	08	08	09	10	10	10
IVd	07	09	09	09	10	10	10	11	12	11	12	13
IVe	04	06	08	04	06	07	09	09	09	09	11	11
IVf	09	11	13	10	12	14	08	09	10	09	11	13
IVg	05	07	07	06	06	08	08	10	10	07	07	07
IVh	06	07	09	04	06	08	12	12	13	10	10	12
IVi	05	05	07	04	05	05	09	11	13	10	13	15
IVj	09	10	11	11	12	13	13	14	16	13	13	15
Ampicillin	07	10	12	11	13	15	14	15	17	09	11	14

APPLICATIONS

All the newly synthesized compounds were active against all the tested strains. Among all the synthesized compounds **IVa, IVf, IVj** shows excellent activity against gram +ve and gram –ve bacteria, remaining all the compounds shows moderate activity against gram +ve and gram –ve bacteria. These compounds **IVa, IVf, IVj** can be used as future antibacterial agents.

CONCLUSIONS

In conclusion, we have synthesized new 12-[4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-phenyl]-8,9,10,12-tetrahydro-benzo[a]xanthen-11-one derivatives **(IVa-j)** through a three-component one-pot reaction of substituted 4-(1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-benzaldehydes, 2-naphthol and substituted dimedones. All the synthesized compounds showed good antibacterial activity.

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