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Characterization and Biological Screening of Newly Synthesized Derivatives of Coumarin

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Abstract: ***It is well known that coumarins show variety of biological properties. In addition to this five membered heterocycles like triazole, thiazolidinone and oxazolidinone are also biologically active. Referring our previous work, which exhibited antimicrobial activity to 1,3,4-oxadiazole group of 3-carbethoxy-2-oxo-2H-benzopyran, in this scheme we carried out the synthesis of new derivatives like triazol, imine, thiazolidinone and oxazolidinone on coumarin. All the synthesized compounds established on the basis of spectral techniques and evaluated for their antimicrobial study.***

Keywords: 1,3,4-Oxadiazole, Triazole, Thiazolidinone, Oxazolidinone

1. Introduction

Antimicrobial drugs have caused an intense revolution, not only in the treatment of infectious diseases but helped a lot for development of public health. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in the past years multidrug resistant microorganisms became an unsolved query for clinical field. Therefore, synthesis of new anti-infective compounds has become an essential need for the treatment of microbial diseases. It has been found out that coumarin and its derivatives represent one of the most active classes of compounds which exhibit diverse biological activities. Coumarin and its derivatives have activities like anti-inflammatory [1], antitubercular [2], antipyretic [3], antimicrobial [4], analgesic [5], cytotoxic [6] and antioxidant [7]. It was also noticed that heterocycles like triazole, imine, thiazolidinone and oxazolidinone documented remarkably for their antimicrobial activity. By integrating all above information, we focused on amalgamation of triazole, imine, thiazolidinone, oxazolidinone and coumarin groups together to develop novel molecules of with value-added characteristics.

2. Experimental Section

Materials and Methods

Materials

All commercial reagents and solvents were procured from S.D. Fine. The reactions were monitored by TLC using on 0.25 mm E-Merck silica gel plates, which were visualized in Iodine Chamber and if needed in UV light. Melting points were taken in open capillaries and are uncorrected. ^{1}H spectra in DMSO-d_6 were recorded on VXR-300 MHz using TMS as internal standard.

Experimental

Synthesis of Compounds

3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran 2(a-b)

Previously synthesized 3-[5′-(1*H*-indol-2″-yl)-1′,3′,4′-oxadiazol-2′-yl]-2-oxo-*2H*-benzopyran **1(a-b)** (0.01 mol) and hydrazine hydrate (0.015 mol) was refluxed in n-butanol for about 4 h. The solvent and the excess hydrazine hydrate were removed under reduced pressure, the residue washed with ether, then recrystallized to give the product 3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-*2H*-benzopyran **2(a-b)** was dried and recrystalized from alcohol.

3-[4′-benzylideneamino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran 3(a-b)

A mixture of equimolar amount of **2(a-b)** 3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-*2H*-benzopyran (0.01 mol) and benzaldehyde (0.01 mol) were refluxed in ethanol for 4 h.. Reaction mass was cooled and poured on to ice piece to obtain the product 3-[4′-benzylideneamino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran **3(a-b)**, which was then filtered, dried and recrystalized from alcohol.

3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one 4(a-b)

In aspiration to synthesize compound **4(a-b)**, thioglycolic acid (0.01 mol) and **3(a-b)** were mixed together in 1,4-dioxane in presence of $ZnCl_2$ as a catalyst and refluxed about 3 h. Then reaction mass was cooled and poured on to ice piece, to obtain the product 3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one **4(a-b)**. Then this product was filtered, dried and recrystalized to obtain pure product.

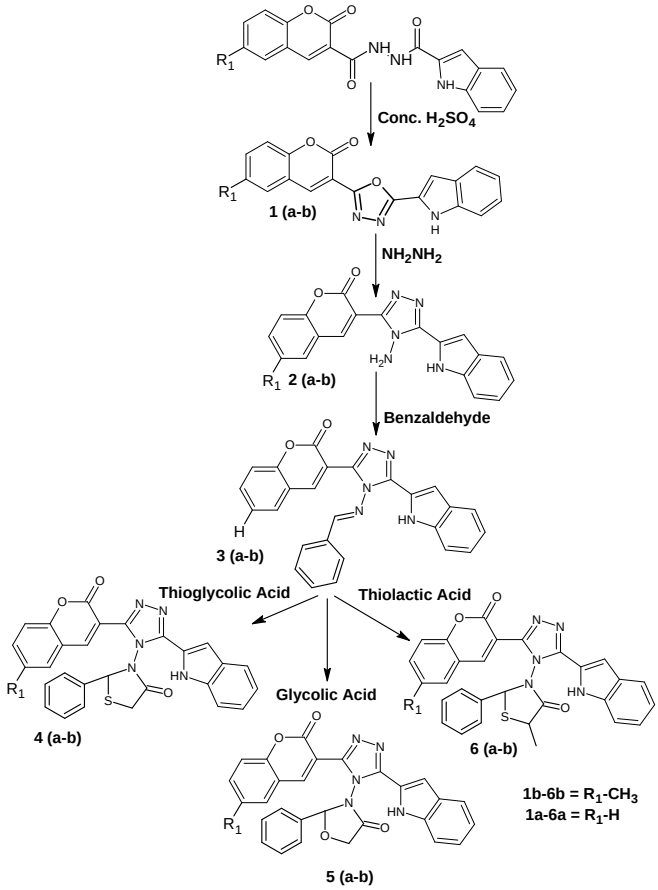
3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-oxazolidin-4″-one 5(a-b)

To synthesize compound **5(a-b)**, glycolic acid (0.01 mol) and **3(a-b)** (0.01 mol) were mixed together in 1,4-dioxane in presence of $ZnCl_2$ as a catalyst. Reaction mass was refluxed about 3 h. Reaction mass was cooled and poured on to ice piece, to obtain the product, which filtered, recrystalized from alcohol to obtain pure product 3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-oxazolidin-4″-one **5(a-b)**.

5″-Methyl-3″-[3′-(2-oxo-2-*H*-benzopyran)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one 6(a-b)

Mixture of Thiolactic acid (0.01 mol) and **3(a-b)** (0.01 mol) in toluene was refluxed over oil bath about 4 h. till the completion of reaction, which was monitored by TLC. Then reaction mass cooled and poured on to ice piece, to obtain the product, which was filtered, recrystalized in presence of alcohol to obtain pure product 5″-methyl-3″-[3′-(2-oxo-2-*H*-benzopyran)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one **6(a-b)**.

Scheme I



3. Characterization of Synthesized Compounds

2(a): 3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran
Molecular Formula: $C_{19}H_{13}N_5O_2$, Molecular Weight: 343, Melting Point: 192°c, Yield: 71%, Elemental Analysis% (Calculated) Found: C (66.47) 66.44, H (3.82) 3.85, N (20.40) 20.38, IR (KBr): 3318 (NH), 3232-3143 (NH_2), 2880, 1759 (C=O), 1685, 1563, 1190, 1070 cm^{-1}, ^1H NMR (DMSO-d_6): δ 5.98 (s, 1H, >NH, D_2O exchangeable), 6.87-7.38 (m, 9H, Aromatic-H), 7.81 (s, 1H, C_4-H), 9.01 (s, 2H, -NH_2, D_2O exchangeable)

2(b): 3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-6-methyl-2-oxo-2-*H*-benzopyran
Molecular Formula: $C_{20}H_{15}N_5O_2$, Molecular Weight: 357, Melting Point: 219°c, Yield: 68%, Elemental Analysis% (Calculated) Found: C (67.22) 67.18, H (4.23) 4.24, N (19.60) 19.63, IR (KBr): 3319 (NH), 3231-3137 (NH_2), 2875, 1760(C=O), 1678 1552, 1190, 1061 cm^{-1}, ^1H NMR (DMSO-d_6): δ 2.29 (s, 3H, C_6-CH_3), 5.95 (s, 1H, >NH, D_2O exchangeable), 6.81-7.29 (m, 8H, Aromatic-H), 7.83 (s, 1H, C_4-H), 8.86 (s, 2H, -NH_2, D_2O exchangeable)

3(a): 3-[4′-benzylideneamino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran
Molecular Formula: $C_{26}H_{17}N_5O_2$, Molecular Weight: 431, Melting Point: 234°c, Yield: 67%, Elemental Analysis% (Calculated) Found: C (72.38) 72.36, H (3.97) 3.99, N (16.23) 16.25, IR (KBr): 3311(NH), 1743(C=O), 1679, 1578, 1510, 1314, 1072, 822 cm^{-1}, ^1H NMR (DMSO-d_6): δ 5.93 (s, 1H, >NH, D_2O exchangeable), 6.92-7.39 (m, 14H, Aromatic-H), 7.80 (s, 1H, C_4-H), 8.18 (s, 1H, HC=N)

3(b): 3-[4′-benzylideneamino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-6-methyl-2-oxo-2-*H*-benzopyran
Molecular Formula: $C_{27}H_{19}N_5O_2$, Molecular Weight: 445, Melting Point: 251°c, Yield: 66%, Elemental Analysis% (Calculated) Found: C (72.80) 72.81, H (4.30) 4.32, N (15.72) 15.70, IR (KBr): 3316 (NH), 1745 (C=O), 1686, 1587, 1506, 1311, 1068, 825 cm^{-1},^1H NMR (DMSO-d_6): δ 2.32 (s, 3H, C_6-CH_3), 5.96 (s, 1H, >NH, D_2O exchangeable), 6.81-7.35 (m, 13H, Aromatic-H), 7.77 (s, 1H, C_4-H), 8.15 (s, 1H, HC=N-)

4(a): 3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one
Molecular Formula: $C_{28}H_{19}N_5O_3S$, Molecular Weight: 505, Melting Point: 267°c, Yield: 62%, Elemental Analysis% (Calculated) Found: C (66.52) 66.50, H (3.79) 3.80, N (13.85) 13.86, S (6.34) 6.36, IR (KBr): 3377 (NH), 2888, 1748 (C=O), 1684, 1561, 1489, 1233, 1108, 978 cm^{-1}, ^1H NMR (DMSO-d_6): δ 3.76 (s, 2H, H_2C-S, thiazolidinone ring), 5.87 (s, 1H, >NH, D_2O exchangeable), 6.09 (S, 1H, >N-CH-Ar), 6.90-7.40 (m, 14H, Aromatic-H), 7.81 (s, 1H, C_4-H)

4(b): 3″-[3′-(6-methyl-2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one
Molecular Formula: $C_{29}H_{21}N_5O_3S$, Molecular Weight: 519, Melting Point: 273°c, Yield: 65%, Elemental Analysis% (Calculated) Found: C (67.04) 67.06, H (4.07) 4.11, N (13.48) 13.50, S (6.17) 6.14, IR (KBr): 3371 (NH), 2891, 1755 (C=O), 1688, 1560, 1494, 1224, 1111, 980 cm^{-1}, ^1H NMR (DMSO-d_6): δ 2.27 (s, 3H, C_6-CH_3), 3.81 (s, 2H, H_2C-S, thiazolidinone ring), 5.90 (s, 1H, >NH, D_2O exchangeable), 6.12 (S, 1H, >N-CH-Ar), 6.79-7.36 (m, 14H, Aromatic-H), 7.80 (s, 1H, C_4-H)

5(a): 3″-[3′-(2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-oxazolidin-4″-one
Molecular Formula: $C_{28}H_{19}N_5O_4$, Molecular Weight: 489, Melting Point: 215°c, Yield: 64%, Elemental Analysis% (Calculated) Found: C (68.71) 68.73, H (3.91) 3.89, N (14.31) 14.33, IR (KBr): 3369 (NH), 2878, 1757 (C=O), 1687, 1601, 1227, 1120, 1005, 840 cm^{-1}, ^1H NMR (DMSO-d_6): δ 4.19 (s, 2H, H_2C-O, oxazolidinone ring), 5.91 (s, 1H,

>NH, D_2O exchangeable), 6.21 (S, 1H, >N-CH-Ar), 6.82-7.36 (m, 14H, Aromatic-H), 7.79 (s, 1H, C_4-H)

5(b): 3″-[3′-(6-methyl-2-oxo-2-*H*-benzopyran-3-yl)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-oxazolidin-4″-one
Molecular Formula: $C_{29}H_{21}N_5O_4$, Molecular Weight: 503, Melting Point: 233°c, Yield: 65%, Elemental Analysis% (Calculated) Found: C (69.18) 69.21, H (4.20) 4.19, N (13.91) 13.93, IR (KBr): 3374 (NH), 2881, 1753 (C=O), 1727, 1681, 1596, 1221, 1127, 1001, 836 cm^{-1}, ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, C_6-CH_3), 4.23 (s, 2H, H_2C-O, oxazolidinone ring), 5.88 (s, 1H, >NH, D_2O exchangeable), 6.17 (S, 1H, >N-CH-Ar), 6.80-7.43 (m, 13H, Aromatic-H), 7.81 (s, 1H, C_4-H)

6(a): 5″-methyl-3″-[3′-(2-oxo-2-*H*-benzopyran)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one
Molecular Formula: $C_{29}H_{21}N_5O_3S$, Molecular Weight: 519, Melting Point: 240°c, Yield: 61%, Elemental Analysis% (Calculated) Found: C (67.04) 67.02, H (4.07) 4.10, N (13.48) 13.50, S (6.17) 6.14, IR (KBr): 3368 (NH), 2887, 1751 (C=O), 1671, 1575, 1491, 1247, 1335, 1057 cm^{-1}, ^1H NMR (DMSO-d_6): δ 1.45 (d, *J*-6*Hz*, 3H, -CH_3), 4.52 (q, 1H, >CH-CH_3), 5.91 (s, 1H, >NH, D_2O exchangeable), 6.17 (S, 1H, >N-CH-Ar), 6.86-7.37 (m, 14H, Aromatic-H), 7.77 (s, 1H, C_4-H)

6(b): 5″-methyl-3″-[3′-(6-methyl-2-oxo-2-*H*-benzopyran)-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-4′-yl]-2″-phenyl-1″,3″-thiazolidin-4″-one Molecular Formula: $C_{30}H_{23}N_5O_3S$, Molecular Weight: 533, Melting Point: 255 °c, Yield: 63%, Elemental Analysis% (Calculated) Found: C (67.53) 67.55, H (4.34) 4.31, N (13.12) 13.15, S (6.01) 6.02, IR (KBr): 3374 (NH), 2884, 1758 (C=O), 1664, 1571, 1488, 1242, 1330, 1051 cm^{-1}, ^1H NMR (DMSO-d_6): δ 2.29 (s, 3H, C_6-CH_3), 1.44 (d, *J*-6, 3H, -CH_3), 4.50 (q, 1H, >CH-CH_3), 5.94 (s, 1H, >NH, D_2O exchangeable), 6.23 (S, 1H, >N-CH-Ar), 6.77-7.34 (m, 14H, Aromatic-H), 7.80 (s, 1H, C_4-H)

4. Antimicrobial Study

All the synthesized compounds **2 (a-b)**, **3 (a-b)**, **4 (a-b)**, **5 (a-b)** and **6 (a-b)** were screened for their antibacterial activity against Gram negative strain, *S. typhi, E. coli* and Gram positive strain *S. aureus*. Study carried out at four different concentrations 200, 150, 100 and 50µg/ml. The standard drugs used for comparison were streptomycin.

Table 1: Antibacterial activity

Compound no.	*S. typhi*	*E. coli*	*S. aureus*
2a	50	100	100
2b	50	100	50
3a	100	100	150
3b	100	50	50
4a	50	100	50
4b	50	50	50
5a	100	50	100
5b	50	50	100
6a	50	100	100
6b	50	50	100

Structure-activity relationship

It is revealed that most of the derivatives are active towards the gram positive and gram negative bacteria at different concentrations. Detail study of antimicrobial screening shows that derivatives **2b**, **3b**, **4a**, **4b**, **5b** and **6b** exhibit significant biological activity, whereas derivatives **2a**, **5a** and **6a** with moderate activity and compound **3a** with reasonable biological activity. Looking towards the pattern of biological screening it is observed that, five membered heterocyclic ring and electron donating methyl group together enhanced the biological activity of synthesized derivatives.

5. Result and Discussion

Previously synthesized [(2-oxo-*2H*-benzopyran-3-yl)carbonyl]-1*H*-indol-2-carbohydrazide was treated with conc. sulfuric acid to give 3-[5′-(1*H*-indol-2″-yl)-1′,3′,4′-oxadiazol-2′-yl]-2-oxo-*2H*-benzopyran 1(a), this compound used as precursor molecule for the total synthesis. In next step hydrazine hydrate was mixed with compound (1a) and refluxed to yield 3-[4′-amino-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran (2a). The IR spectrum of compound (2a) showed band at 3315, 3228 and 3140 cm^{-1} for NH and NH_2. The ^1H-NMR of (2a) showed the presence of signal at δ 9.01 and 5.98 for the protons of -NH_2 and -NH respectively, which were D_2O exchangeable, it indicated that oxadiazole ring system is transformed to triazole. To prepare Schiff's base, compound (2a) was further treated with benzaldehyde to give 3-[4′-benzylideneamino]-5′-(1*H*-indol-2″-yl)-4*H*-1′,2′,4′-triazol-3′-yl]-2-oxo-2-*H*-benzopyran (3a), IR spectra of compound showed loss of band for NH_2, whereas ^1H NMR of compound showed additional singlet at δ 8.18 for one proton of HC=N. Finally with an intention to prepare thiazolidinone and oxazolidinone derivatives, compound (3a) was condensed with thioglycolic, glycolic and thiolactic acid to give (4a), (5a) and (6a). Compounds (4a) and (5a) in their ^1H NMR spectrum showed singlet at δ 3.76 for two protons of H_2C-S and δ 4.19 for two protons of H_2C-O respectively. Compound (6a) showed doublet at δ 1.45 for three protons and quartrate at δ 4.52 for one proton. The structures of all above compounds and other derivatives were confirmed by their spectral data and physical properties. At last synthesized derivatives tested against gram positive and gram negative bacteria for their biological activity.

6. Conclusion

Present scheme comprises of synthetic route for preparation of triazole, thiazolidinone and oxazolidinone derivatives from coumarin. Spectral data ratifies the structure of all synthesized compounds. The notable antimicrobial activity of certain compounds confirms that these are good findings for the making of new active coumarin derivatives.

7. Future Scope of the Study

The present study has focused on exploring the synthesis of novel coumarin derivatives and their characterization.

Efforts were made to study the therapeutic activities of new coumarin derivatives as, the heterocyclic compounds containing sulphur, nitrogen, oxygen show the therapeutic activities such as anti-inflammatory, antifungal, anticancer, analgesic, antipyretic, anti-bacterial and antihelmintic and anti-tubercular. These entities may also be used as intermediates in other drugs synthesis.

8. Acknowledgment

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