IJBPAS, February, 2025, 14(2): 793-802

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

SYNTHESIS, CHARACTERIZATION OF UMBELLIFERONE CONTAINING OXAZINE DERIVATIVES AND THEIR PHARMACOLOGICAL PROPERTIES

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Received 4th Nov. 2023; Revised 5th Dec. 2023; Accepted 2nd May 2024; Available online 1st Feb. 2025

https://doi.org/10.31032/IJBPAS/2025/14.2.8692

ABSTRACT

Using the condensation-cyclization reaction between paraformaldehyde with different amines in methanol at reflux, derivatives of umbelliferone-oxazine were produced and verified using spectrum studies. Promising outcomes were seen in microbial testing against a range of bacterial and fungal species. Adsorption Distribution Metabolism Excretion(ADME) evaluation of these medications was carried out. Title compounds demonstrated excellent drug absorption in cells and passed the ADME test.

Keywords: Umbelliferone, Oxazine, Antimicrobial screening, ADME studies

INTRODUCTION:

Novel Coumarin (Umbelliferone) amino compounds have potent antiviral properties. The H1N1 influenza A virus was prevented from replicating by methylamino derivatives **[1]**. Certain Coumarin Oxime Ethers exhibit mild levels of toxicity in addition to their anti-tubercular properties. It was discovered that derivatives exhibiting anti-tubercular properties also cleave and hence display nuclease activity **[2]**. Novel Thiazolyl Coumarin compounds reduce profibrotic effects on cardiac fibroblasts and inhibit HDAC activity **[3]**. In comparison to other medications, 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide has reduced toxicity and exhibits anti-proliferative effect

in stomach cancer **[4]**. Strong cytotoxic and cytostatic effects were shown in the in-vitro research of several nitrogen-containing coumarin derivatives against lymphoblastic cell line, gastric cancer, colon cancer, hepatoma, renal cancer, and other cancer cells **[5]**. Derivatives of isooxazoline5 linked to coumarins are similarly efficient against cancerous cells **[4-5]**. Better effectiveness against bacteria or microorganisms is provided by nitrogen-containing coumarin, such as coumarin with a thiazole ring **[6]**. Furthermore, it was found that a few synthetic derivatives of methotrexate, such as the benzoxazine moiety, were safe and effective options for antirheumatic drugs **[7]**. Utilizing benzoxazine derivatives as intermediates, other heterocyclic structures of biological importance have also been synthesized **[8]**. It has been discovered that benzoxazine derivatives, especially those with a 1,3-position, may exhibit antibacterial, antifungal, antiproliferative, and antimicrobial properties **[9–15]**. 6-arylbenzoxazines have also been characterized as potent non-steroidal progesterone receptor agonists **[16]**. Numerous imidazole derivatives of 1,4-benzothiazine and 1,4-benzoxazine were synthesized and evaluated for their antifungal activity against a mouse experimental model of candidiasis; nevertheless, in vitro action was often absent **[17–20]**. We made the decision to synthesize benzoxazine derivatives and investigate their antibacterial activity in light of their potential medical use. An analysis of the absorption, distribution, metabolism, and excretion of manufactured benzoxazine analogues was done as part of the ADME investigation.

METHODS AND MATERIALS:

The solvents and chemicals are all indented from Sigma Aldrich. The glass capillary technique was used to test the uncorrected melting points of the generated compounds. The Bruker IR Spectrometer was used to record IR spectra. The readings of the elemental analysis were within 0.4% of the theoretical values. 1H NMR was acquired using a Bruker TD-65536 NMR (400MHz) with tetramethyl silane serving as an internal standard and deuterated dimethyl sulfoxide (DMSO) and deuterated chloroform (CDCl3) as solvents.

Synthesis of 7-hydroxy-4-methyl-2H-chromene-2-one **(2)**:

The compound **(2)** was prepared according to the literature **[21]**. The compound **(1)** was reacted with ethyl acetoacetate in the presence of conc. H_2SO_4 to provide the compound **(2)** .

General procedure of Umbelliferone-oxazine derivatives**(4a–4f)**:

Paraformaldehyde (2gm, 33mmol), primary amine **3a – 3f** (15mmol) and Methanol (15mL) in a 150 mL-3N-RBF. Then add 7-hydroxy-4-methylbenzopyron-2[H]-one**(2)** (2.91 gm, 15 mmol) (Lit[21]) in above reaction mixture. The reaction mixture refluxed for 6 Hr. Reaction completion was checked by TLC. The reaction mixture allows to cool at 30-35°C and dried with anhydrous sodium sulphate. RM was filtered and distilled under vacuum till dryness. Obtained crude crystallized from ethanol to yield title compounds **(4a–4f)**.

4-methyl-9-phenyl-9,10-dihydro-2H,8H-benzopyrone[8,7- e][1,3]oxazine (**4a**)

Yield: 70%, m.p. 135°C. IR (KBr) cm^{-1}: 1731.12, 1433.40, 1356.60, 1314.12, 1265.79, 1215.25, 1057.73, 980.65. ^1H NMR (400MHz, DMSO-d_6) δ, ppm: 7.25 (1H, d, C(5)H); 7.15 (2H, d, (C(3)H , C(5)H); 7.10 (2H, d, (C(2)H, C(6)H); 6.90 (1H, t, C(4)H); 6.76 (1H, d, C(6)H); 6.11 (1H, s, CH); 6.99 (2H, s, CH_2); 4.47 (2H, s, CH_2); 2.43 (3H, s, CH_3). EI-MS Mass calculated for $C_{18}H_{15}NO_5$ (m/z): 293.31, found $[M]^+$: 293.2. Elemental analysis Found: C, 73.70; H, 5.01; N, 4.75; O, 16.54.

4-(4-methyl-2-oxo-2H,8H-chromeno[8,7-e][1,3]benzopyrone-9(10H)-yl)benzoicacid (**4b**)

Yield: 62%, m.p. 130°C. IR (KBr) cm^{-1}: 2929.94, 2360.02, 2339.20, 1698.61, 1681.08, 1651.14, 1604.14, 1558.11, 1541.49, 1454.43, 1360.57, 1136.70, 1066.23. ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.52 (3H, d, C(5)H, (C(2)H, C(6)H); 6.99 (2H, s, CH_2); 6.88 (3H, d, C(6)H, (C(3)H , C(5)H); 6.17 (1H, s, CH); 4.47 (2H, s, CH_2); 2.43 (3H, s, CH_3); 12.52 (1H, broad, s, COOH). EI-MS Mass calculated for $C_{19}H_{15}NO_5$ (m/z): 337.32, found $[M]^+$: 337.10. Elemental analysis found: C, 67.61; H, 4.49; N, 4.10; O, 23.80.

4-methyl-9-(3-nitrophenyl)-9,10-dihydro-2H,8H-benzopyrone[8,7-e][1,3]oxazine (**4c**)

Yield: 78%, m.p. 110°C. IR (KBr) cm^{-1}: 2919.70, 2359.70, 1676.72, 1560.98, 1452.78, 1316.28, 1207.47, 1066.43, 980.73, 908.68. ^1H NMR (400MHz, DMSO-d_6) δ, ppm: 7.87 (2H, d, C(5)H, C(6)H); 7.61 (2H, t, (C(2)H , C(4)H); 7.44 (1H, t, C(5)H); 6.99 (2H, s, CH_2); 6.17 (1H, s, CH); 7.04 (1H, d, C(6)H); 5.24 (2H, s, CH_2); 2.42 (3H, s, CH_3). EI-MS Mass calculated for $C_{18}H_{14}N_2O_5$ (m/z): 338.31, found $[M]^+$: 338.50. Elemental analysis found: C, 63.89; H, 4.10; N, 8.30; O, 23.71.

4-methyl-9-(4-nitrophenyl)-9,10-dihydro-2H,8H-benzopyrone[8,7-e][1,3]oxazine (**4d**)

Yield: 75%, m.p. 107°C. IR (KBr) cm^{-1}: 2919.70, 2359.70, 1676.72, 1513.26, 1390.41, 1316.26, 1207.47, 1136.60, 1066.43, 980.73.

^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 8.12 (2H, d, (C(2)H , C(4)H); 7.72 (1H, d, C(5)H); 7.00 (3H, d, C(6)H, (C(3)H, C(5)H); 6.17 (1H, s, CH); 6.01 (2H, s, CH_2); 4.82 (2H, s, CH_2); 2.42 (3H, s, CH_3). EI-MS Mass calculated for $C_{18}H_{14}N_2O_5$ (m/z): 338.31, found $[M]^+$: 338.13. Elemental analysis found: C, 63.92; H, 4.10; N, 8.25; O, 23.73.

4-methyl-9-(p-tolyl)-9,10-dihydro-2H,8H-benzopyrone[8,7-e][1,3]oxazine (**4e**)

Yield: 65%, m.p. 160°C. IR (KBr) cm^{-1}: 3023, 2883, 1713, 1596, 1512, 1493.1H NMR (400 MHz, CDCl3) δ, ppm: 7.36 (1H, d, C(5)H); 7.12 (3H, m, C(6)H, C(3)H, C(5)H); 6.77 (2H, d, C(2)H, C(6)H); 6.12 (1H, s, CH); 5.41 (2H, s, CH_2); 4.79 (2H, s, CH_2); 2.37 (3H, s, CH_3); 2.26 (3H, s, CH_3). EI-MS Mass calculated for $C_{19}H_{18}O_3N$ (m/z) 308.12 found $[M]^+$: 308.8. Elemental analysis found: C, 74.20; H, 5.50; N, 4.49; O, 15.81.

4-(4-methyl-2-oxo-2H,8H-benzopyrone[8,7-e][1,3]oxazine-9(10H)-yl)benzenesulfonic acid (**4f**)

Yield: 60%, m.p. 125°C. IR (KBr) cm^{-1}: 2360.19, 1675.53, 1601.17, 1451.80, 1437.33, 1361.26, 1316.09, 1266.77, 1136.42, 1066.10, 980.95, 841.74. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.51 (1H, d, C(5)H); 7.26 (2H, d, C(2)H, C(6)H); 7.04 (2H, s, CH_2); 8.61 (1H, broad, s, SO_3H); 6.91 (3H, d, C(6)H, (C(3)H, C(5)H); 6.16 (1H, s, CH); 4.38 (2H, s, CH_2); 2.43 (3H, s, CH_3). EI-MS Mass calculated for $C_{18}H_{15}NO_6S$ (m/z): 373.38, found $[M]^+$: 373.40. Elemental analysis found: C, 57.89; H, 4.01; N, 3.72; O, 25.69; S, 8.69.

RESULT & DISCUSSION:

The process of condensing 7-hydroxy-4-methylchromen-2-one with aromatic amines yields analogs of umbelliferone-Oxazine. The validity of the compound's structural interpretation might be confirmed through the use of spectrum analysis techniques such as ^{1}H NMR and IR. Melting points were acquired. Every functional group found in title compounds is supported by the IR data. The hydroxy group (-OH) at position 7 is removed so the cyclization occurs, and the absence of hydroxyl group frequency in IR and the peak of the -OH group in the ^{1}H NMR of the molecule suggest the formation of umbelliferone-oxazines. Together with activity data, more research on a substance's antibacterial and antifungal properties is included in **Table 1**.

Antimicrobial Activity:

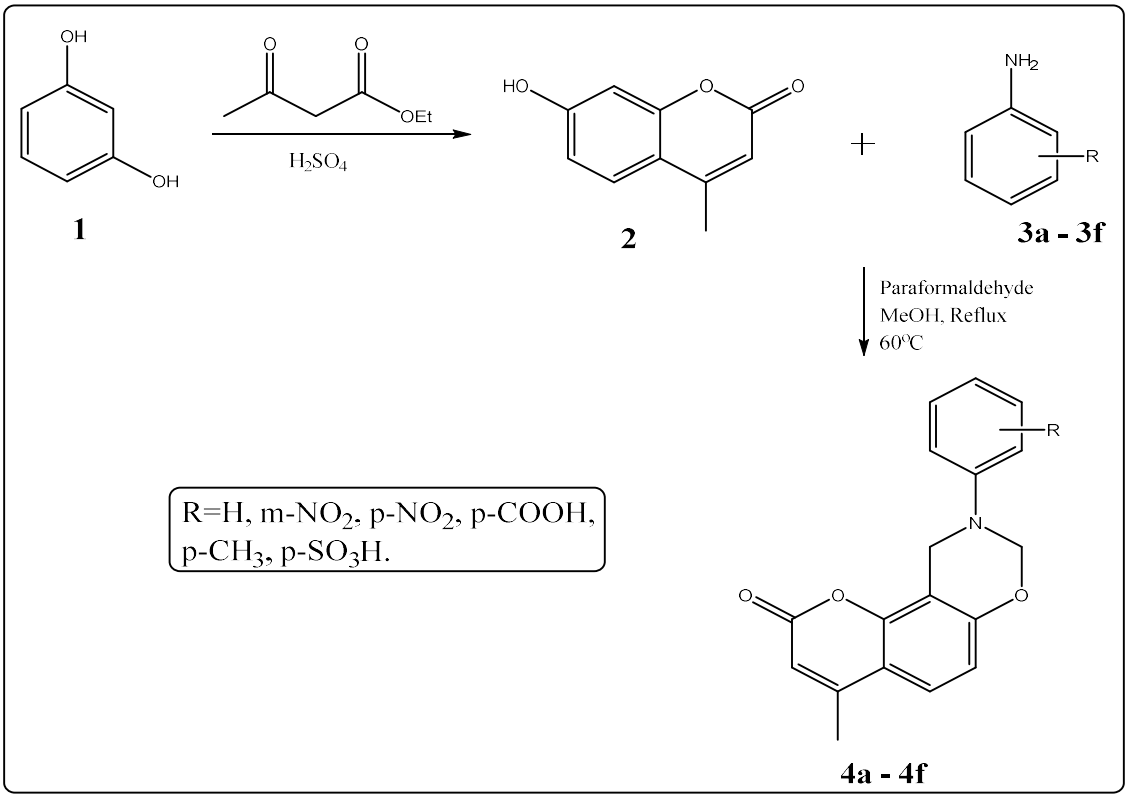

Figure 1: Reaction scheme Synthesis of Umbelliferone-Oxazines Derivatives

Table 1: Zone of inhibition of the synthesized compounds

	Zone of Inhibition in mm					
Compound	***Bacillus subtilis* (gm^{+ve})**	***Staphylococcus aureus* (gm^{+ve})**	***Escherichia coli* (gm^{-ve})**	***Pseudomonas aeruginosa* (gm^{-ve})**	***Aspergillus fumigatus* (fungi)**	***Candida albicans* (fungi)**
4a	**13mm**	**31mm**	**19mm**	**13mm**	**16mm**	**13mm**
4b	**15mm**	**33mm**	**21mm**	**17mm**	**12mm**	**14mm**
4c	**14mm**	**17mm**	**28mm**	**18mm**	**18mm**	**13mm**
4d	**18mm**	**12mm**	**18mm**	**21mm**	**20mm**	**12mm**
4e	**16mm**	**16mm**	**14mm**	**34mm**	**22mm**	**10mm**
4f	**14mm**	**16mm**	**15mm**	**25mm**	**23mm**	**13mm**
Ampicillin	**10mm**	**11mm**	**10mm**	**11mm**	**9mm**	**10mm**

The Kirby-Bauer method **[22]** disk diffusion technique was utilized to screen the antibacterial and antifungal activities of the title compounds against microorganisms. Every synthetic material was diluted with DMSO (dimethyl sulfoxide) (0.2 ml of 10 mg/ml) and then aseptically put to the plates. On plates, the produced compounds were grown using nutrient agar (10mm). Following a 24-hour incubation period at 37°C, the antimicrobial activity was assessed by measuring, using a standard scale, the zones of bacterial and fungal growth inhibition caused by the diffusion of chemicals from the well into the surrounding medium. Each generated compound's antibacterial and antifungal qualities were assessed using the following bacteria and fungi: Aspergillus

fumigatus, Candida albicans; Escherichia coli (gm-ve); Pseudomonas aeruginosa (gm-ve); Staphylococcus aureus (gm+ve); Bacillus subtilis (gm+ve). Gentamicin served as the experiment's usual control drug. Compounds **(4a–f)** in the title show outstanding effectiveness. It was discovered that **4d** was most effective against Bacillus subtilis while 3b was most effective against Candida albicans. It was shown that *Escherichia coli* was susceptible to **4c** and *Pseudomonas aeruginosa* to **4e**. **Table 1** illustrates the effectiveness of Compounds **4a** and **4b** against *Staphylococcus aureus.* The two strongest compounds, **4e** and **4f**, had a greater fungicidal activity on *Aspergillus fumigatus.* Comparing the title compounds to normal ampicillin, they demonstrated substantial inhibitory effects against tested Gram-positive, Gram-negative, and antifungal microorganisms.

ADME Studies:

Using the publicly available web server Swiss ADME, the physical characteristics and the ADME parameters (absorption, distribution, metabolism, and excretion) were determined **[23]**. **Table No. 2** contains the findings of the in silico ADME characteristics of **(4a-f)**. For each chemical, the following five parameters were determined using Lipinski's rule of five: molecular weight (MW), number of hydrogen bond acceptors (nHBA), donors (nHBD), number of rotatable bonds (nRB), and topological polar surface area (TPSA). Lipophilicity (-0.7 < XLOGP3 < 5.0), molecular weight (MW) (150 g mol–1 < MW < 500 g mol–1), solubility (0 < log S (ESOL) < 6) and flexibility (0 < of rotatable bonds < 9) are the criteria taken into account to calculate the score.

Table 2: Swiss ADME results of Umbelliferone-oxazine analogues and standard Ibuprofen and BHT

COMPOUND	4a	4b	4c	4d	4e	4f	Ibuprofen	BHT
MW	293.32	353.37	338.31	338.31	307.34	373.38	206.28	220.35
Rotatable bonds	1	2	2	2	1	2	4	2
H-bond acceptors	3	5	5	5	3	6	2	1
H-bond donors	0	1	0	0	0	1	1	1
MR	88.65	102.53	97.47	97.47	93.62	98.51	62.18	71.97
TPSA	42.68	79.98	88.5	88.5	42.68	105.43	37.3	20.23
Consensus Log P	3.15	2.54	2.57	2.55	3.49	2.25	3	4.24
ESOL Solubility (mg/ml)	1.86E-02	1.03E-02	1.95E-02	1.95E-02	9.86E-03	6.53E-02	9.09E-02	6.00E-03
GI absorption	High	High	High	High	High	High	High	High
BBB permeant	Yes	No	No	No	Yes	No	Yes	Yes
Pgp substrate	No	Yes	No	No	No	No	No	No
Lipinski violations	0	0	0	0	0	0	0	0
Muegge violations	0	0	0	0	0	0	0	2
PAINS alerts	0	0	0	1	1	0	0	0
Leadlikeness violations	0	1	0	0	1	1	1	2

All of the synthesized compounds **(4a–4f)** had a score of 55%, which is high bioavailability, according to the Rule of Five. A log S scale was developed to measure the qualitative solubility of medications that must have a high-water solubility in order to transport active components. If log S is less than -10, it is considered weakly soluble, less than -6, it is moderately soluble, less than -4, it is extremely soluble, less than -2, and less than 0 is very soluble. According to **Table 2**, compounds **(4a)** and **(4e)** have BBB (blood-brain barrier) permeant, whereas derivatives **(4a-f)** have high GI absorption.

CONCLUSION:

Umbelliferone-oxazine derivatives were created by cyclizing 7-hydroxy-4-methyl-chromen-2-one with Paraformaldehyde and the amines. The produced chemicals are successfully examined using TLC, IR, 1HMR, and mass spectroscopy. Effective antifungal and antibacterial capabilities are inhibited by title compounds. The current research and development of novel antifungal and antibacterial medications may benefit from these discoveries. Only a small number of compounds passed the projected toxicity evaluation, which ensures their absorption in the blood-brain barrier, as the title compounds were found to be in the acceptable range and pass the ADME(Adsorption Distribution Metabolism Excretion) examination. The groundwork for the first search for potential novel drugs with minimum toxicity and intriguing biological activity is ensured by our study.

ACKNOWLEDGEMENT:

The authors are thankful to Dr. Devanshu Patel, President, Parul University for providing necessary infrastructure facilitates.

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