Research Article

Journal of Chemistry Letters
journal homepage: www.jchemlett.com
ISSN (online) 2717-1892 (print) 2821-0123

Theoretical Investigation and Design of Novel Cephalosporin Based Inhibitors of a DD-carboxypeptidase Enzyme of *Salmonella typhimurium*

Ameji Philip John[1,*], Adamu Uzairu[2], Gideon Adamu Shallangwa[2], Sani Uba[2]

[1]*Department of Chemistry, Federal University Lokoja, P.M.B., 1154, Lokoja, Kogi State, Nigeria*
[2]*Department of Chemistry, Ahmadu Bello University, P.M.B. 1044, Zaria, Kaduna State Nigeria*

ARTICLE INFO

Article history:
Received 11 September 2022
Received in revised form 6 October 2022
Accepted 5 November 2022
Available online 2 April 2023

Keywords:
PBP6
Salmonella Typhimurium
Drug-likeness
Descriptor
Cephalosporin
QSAR

ABSTRACT

The rising mortality and morbidity associated with *Salmonella typhimurium* induced salmonellosis aggravated by the emergence of multi-drug resistant strains of this pathogenic bacterium has made continuous search for novel antibiotics a necessity. In our quest to design newer drug candidates, a series of cephalosporin analogues with significant bioactivities against the aforementioned bacterium were optimized using Density Functional Theorem (DFT) and subjected to Quantitative Structure-Activity Relationship modelling using Multi-linear Regression to harness the dominant descriptors of the antimicrobial properties of the compounds. The validated model (R^2 = 0.92, R^2_{Adj} = 0.91, Q^2_{LOO} = 0.88, R^2_{pred} = 0.71, LOF = 0.0001) reveals the predominance of SHBint3, SpMin6_Bhe, and L2u descriptors. Molecular docking simulation of the compounds guided by the model led to the design of two novel ligands, L_1 and L_2 with binding affinity of -7.7 kcal/mol and -8.3 kcal/mol, respectively against the PBP6 protein target of the bacterium. These values are higher than the -6.7 kcal/mol obtained for cefuroxime (R) antibiotic used as standard for comparison against the same protein target. The newly designed ligands exhibit excellent pharmacokinetic and toxicological profiles as well positive drug-likeness. Using the generated model, Minimum Inhibitory Concentration values of 0.038µg/mL and 0.051µg/mL were predicted for L_1 and L_2, respectively. The novel ligands displayed a balance of potency, binding affinity, pharmacokinetic and toxicological profiles as well as unique mechanisms of interactions with the PBP6 target of *Salmonella typhimurium*. We therefore recommend their synthesis, biological evaluation and clinical trial.

1. Introduction

Coumarin constitutes one of the great classes of natural compounds. In the well-known family of coumarins, dimeric coumarins (bis coumarins) occupy an interesting position. Although some types of these compounds could be extracted from plants [1] and interest in its chemistry because of its fitness as pharmaceutically activities. Coumarin has been reported to serve as anti-microbial [2], anti-cancer [3], anticoagulant [4], anti-inflammatory [2] agents. These biological activities of coumarins raised our interest in synthesizing some new coumarins.

Water has a unique media in chemistry and is one of the best solvents, owing to its features such as being eco-friendly, clean, green, nontoxic, non-flammable, safe, low-cost and readily available in organic transformations. Also, the use of aqua media not only diminishes the risk entailed in the use of organic solvents but also improves the rate of many chemical reactions [5-8].

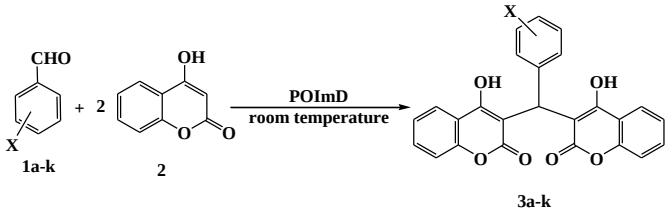
2. Results and Discussion

In continuation of our research for the green synthesis of the spread of neat and efficient procedures for the synthesis of organic and pharmaceutical compounds [9-14], an solvent free, facile and efficient procedure was introduced for the synthesis of bis coumarinylmethane by

* Corresponding author.; Tel. +2347036492681; e-mail: ameji4real55@gmail.com
https://doi.org/10.22034/jchemlett.2022.361586.1085

the POImD catalyzed reaction of two equivalent of 4-hydroxycoumarins and one equivalent of synthesized aldehyde.

Although, synthesis of bis coumarins using catalysts and ionic liquids such as SO_3H-functionalized benzimidazolium cation[15], [bmim]BF_4[16], [MIM$(CH_2)_4SO_3H$][HSO_4] [17], sulfonic acid-functionalized pyridinium chloride[18], choline chloride–oxalic acid [19], $RuCl_3{\cdot}nH_2O$[20] and $NaHSO_4/SiO_2$/Indion 190 resin [21] was reported, However, most of these reported methods suffer from expensive reagents or catalysts, environmental pollution, exotic reaction conditions, long reaction time, complicated operations and unsatisfactory yields. In order to make this reaction simple and green, herein, POImD was used to synthesis of bis coumarinylmethanes by the one-pot reaction of 4-hydroxycoumarin and various benzaldehydes at room temperature.



Scheme 1. Synthesis of bis coumarinylmethanes **3a-k** using POImD at room temperature.

The efficiency of POImD rather than some of other catalysts in their catalytic amount was checked for the synthesis of **3a**. As summarized in Table 1, the best result is related to usage of 0.2mmol% of POImD (Table 1; Entry 11).

Table 1. Effect of catalyst on the synthesis of **3a** at room temperature

Entry	Catalyst	Catalyst amount[a]	Time (min)	Yield (%)
1	HCl	5 drops	360	52
2	*L*-proline	0.1mmol	360	65
3	I_2	0.1mmol	480	48
4	K10	0.1g	210	63
5	$ZnCl_2$	0.1g	360	63
6	[BMIm]Br	0.1mmol	150	67
7	[BMIm]OH	0.1mmol	160	72
8	SiO_2	0.1g	360	63
9	PPI[19]	0.3mmol	120	75
10	POImD	0.3mmol	60	98
11	POImD	0.2mmol	60	98
12	POImD	0.1mmol	120	73

[a]Catalyst amount per 1mmol of aldehyde; [b]solvent in the entries 1-5 and 8-12 was water.

To compare this method with catalyst-free reaction, the achieved yields increased and the reaction times were shortened to 60-90 min. On the other hand, this catalyst showed more satisfactory results rather than catalysts such as Fe_3O_4, SiO_2, K10 montmorillonite and potassium phthalimide (PPI) [19]. Because nucleophilic centers in POImD is more powerful for the ionization of 4-hydroxycoumarin (Scheme 2).

Initially, we carried out the reaction of **1a** and 4-hydroxycoumarin in the presence of 0.002 mol of POImD at room temperature under solvent free reaction. This reaction was carried out with 0.001, 0.002 and 0.003mol of POImD, respectively. The best results were obtained using 0.2mmol of the catalyst with complete conversion within 60 min and in 98% yields (Table 2).

Table 2. Synthesis of biscoumarinylmethane **3a-l** using POImD at room temperature

Entry	Product[a]	X	Time (min)	Yield[b] (%)
1	**3a**	4-NO_2	60	98
2	**3b**	3-NO_2	60	96
3	**3c**	2-NO_2	60	94
4	**3d**	4-Br	60	97
5	**3e**	3-Br	75	90
6	**3f**	4-Cl	60	98
7	**3g**	3-Cl	60	92
8	**3h**	2-Cl	90	90
9	**3i**	4-F	60	92
10	**3j**	3-OH	75	90

[1] ∗ Corresponding author.
Email: Ameji Philip John (ameji4real55@gmail.com)
ORCID ID: 0000-0001-5516-8802

11	**3k**	2-OH	90	87
12	**3l**	-	60	94

[a]All products were characterized by their physical constant, comparison with authentic samples, IR and NMR spectroscopy; [b]Yields based upon starting aldehyde

To expand the scope and generality of this method, some aldehydes were used as substrate in this reaction. The results were summerized in Table 2. In continuation of our studies, we triggered to synthesize tris-(bis coumarinyl)methane using POImD (Figure 1).

All of compounds summarized in Table 2 were characterized by spectroscopic methods (IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis. So, all of synthesized compounds are new. They were prepared from pyrazolecarbaldehydes that most of them are not commercially available material. Our experiments also indicated that after five successive runs, recycled ionic liquid showed no loss of efficiency with regard to reaction time and yield (Table 3).

Table 3. Evaluation of reusability of POImD for the synthesis of **3a**

run	1	2	3	4	5
Time(min)	60	60	60	60	60
Yield(%)	98	96	98	97	96

A possible mechanism for the synthesis of bis (coumarinyl)methane derivatives was proposed (Scheme 2). Initially, 4-hydroxycoumarine (**2**) was converted to active form **6** by hydrogen abstraction in the presence of (POImD **4**). Then, the nucleophilic attack of C-3 of intermediate **6** to carbonyl moiety of arylaldehyde (**1**) lead to compound **7**. Finally, nucleophilic attack of the second molecule of activated 4-hydroxycoumarine to intermediate **7** lead to product **3**. It is mentionable that under this procedure catalyst POImD reversibly converts from **4** to **5**.

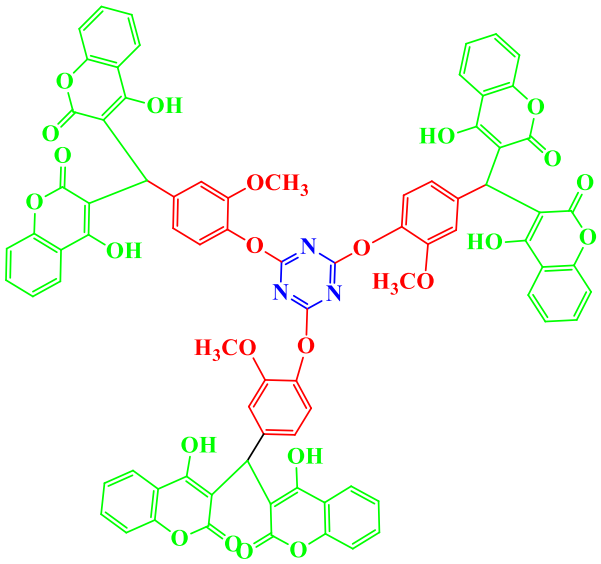
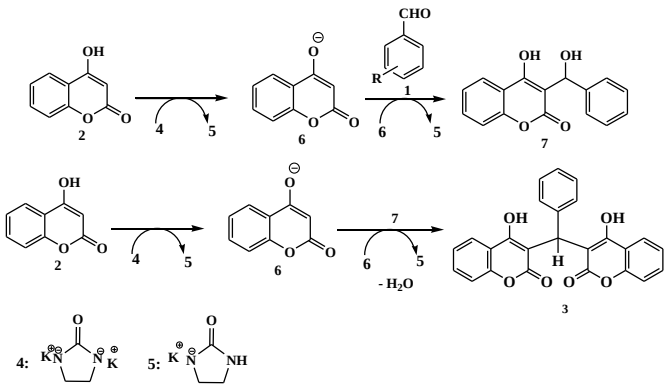


Figure 1. Structure of novel tris-(bis coumarinyl)methane **3l.**



Scheme 2. Proposed mechanism for the synthesis of biscoumarinylmethane using POImD

3. Experimental

3.1. General

Chemicals were purchased from Fluka and Merck. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo FT-IR 8600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 400 DRX Avance instrument at 500 and 125 MHz. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer and

agreed with the calculated values. All solvents used were dried and distilled according to standard procedures.

3.2. General procedure for the synthesis of potassium 2-oxoimidazolidine-1,3-diide (POImD)

A mixture of imidazolidin-2-one (20 mmol), KOH (20 mmol) and H_2O (10 mL) was stirred overnight. Following the completion of the reaction, as indicated by TLC, potassium 2-oxoimidazolidine-1,3-diide (POImD) was separated from the reaction mixture by filtration. POImD was purified by recrystallization from EtOH to afford pure products [9].

*3.3. General procedure for the synthesis of Compounds **3a-l***

A mixture containing aldehyde (1 mmol), 4-hydroxycoumarin (2 mmol), 2mmol% of POImD and 10mL H_2O were stirred at room temperature for the required reaction times. The progress of the reaction was monitored by TLC (EtOAc: petroleum ether 1:3). Having completed the reaction, we extracted the product with $CHCl_3/H_2O$. After separation of phases and evaporation of the organic phase and recrystallization of the residue, the pure product was obtained. The aqueous phase was concentrated under reduced pressure to recover the catalyst for subsequent use.

3,3'-((4-nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 1)*: Yellow solid; m.p. = 234-236 ˚C; FT-IR: ν_{max} (KBr): 3433, 1662, 1561, 1608, 1520, 1348, 1103 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.40 (s, 1H), 6.84 (s, br, 2H), 7.30-7.42 (m, 6H), 7.58 (s, br, 2H), 7.88 (d, *J*= 6.7 Hz, 2H), 8.08 (d, *J*= 6.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ= 36.8, 103.4, 116.0, 118.5, 123.3, 123.7, 124.1, 128.2, 131.9, 145.6, 150.1, 152.5, 164.5, 166.4 ppm. Anal Calc. for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.63; H, 3.29; N, 3.08.

3,3'-((3-nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 2)*: Off white solid; mp 234-236 ˚C; FT-IR: ν_{max} (KBr): 3428, 3079, 1658, 1611, 1564, 1528, 1347, 1102, 1058 cm^{-1},^{1}H NMR (400 MHz, DMSO-d_6): δ= 7.27-7.35 (m, 4H), 7.50-7.57 (m, 4H), 7.86 (d, *J*= 8.0 Hz, 1H), 7.92 (s, 1H), 8.03 (d, *J*= 8.0 Hz, 1H). Anal Calc. for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.64; H, 3.29; N, 3.07.

3,3'-((2-nitrophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 3)*: Off white solid; m.p. = 245-247 ˚C; FT-IR: ν_{max} (KBr): 3429, 3075, 2930, 1656, 1609,1562, 1354, 1522, 1069 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 5.14 (s, 1H), 7.26-7.33 (m, 4H), 7.40 (d, *J*= 7.6 Hz, 2H), 7.42-7.58 (m, 3H), 7.66 (d, *J*= 7.6 Hz, 1H), 7.84 (d, *J*= 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 34.4, 103.6, 116.1, 117.7, 123.7, 123.8, 124.1, 127.2, 130.0, 131.9, 132.2, 134.7, 149.5, 152.3, 163.4, 165.0. Anal Calc. for $C_{25}H_{15}NO_8$: C, 65.65; H, 3.31; N, 3.06. Found: C, 65.63; H, 3.33; N, 3.05.

3,3'-((4-bromophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 4)*: Off white solid; m.p. = 285-287 ˚C; FT-IR: ν_{max} (KBr): 3421, 3071, 2938, 1669, 1610, 1561, 1488, 1096, 765 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.33 (s, 1H), 7.12 (d, *J*= 8.0 Hz, 2H), 7.34-7.42 (m, 4H), 7.59 (t, *J*= 7.6 Hz, 4H), 7.90 (d, *J*= 7.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 35.8, 104.0, 116.1, 117.9, 118.7, 123.9, 124.0, 129.2, 131.0, 132.1, 139.7, 152.3, 164.8, 165.4. Anal Calc. for $C_{25}H_{15}BrO_6$: C, 61.12; H, 3.08. Found: C, 61.14; H, 3.10.

3,3'-((3-bromophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 5)*: Off white solid; m.p. = 242-244 ˚C; FT-IR: ν_{max} (KBr): 3421, 3074, 1664, 1609, 1561, 1498, 1095, 765 cm^{-1},^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.35 (s, 1H), 7.10 (s, br., 3H), 7.31-7.36 (m, 7H), 7.58 (t, *J*= 7.2 Hz, 2H), 7.90 (d, *J*= 7.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 36.1, 103.7, 116.0, 118.1, 121.7, 123.8, 124.0, 126.1, 128.6, 129.4, 130.3, 132.0, 143.6, 152.3, 164.7, 165.7. Anal Calc. for $C_{25}H_{15}BrO_6$: C, 61.12; H, 3.08. Found: C, 61.10; H, 3.07.

3,3'-((4-chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 6)*: Off white solid; m.p. = 256-258 ˚C; FT-IR: ν_{max} (KBr): 3434, 1668, 1613, 1562, 1495, 1093, 767 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.28 (s, 1H), 7.14 (d, *J*= 8.0 Hz, 2H), 7.24-7.35 (m, 6H), 7.57 (t, *J*= 8.0 Hz, 2H), 7.88 (d, *J*= 8.0 Hz, 2H). Anal Calc. for $C_{25}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.22; H, 3.35.

3,3'-((3-chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 7)*: Off white solid; m.p. = 233-235 ˚C; FT-IR: ν_{max} (KBr): 3398, 3074, 1665, 1610, 1562, 1489, 1098, 764 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.34 (s, 1H), 7.12-7.37 (m, 10H), 7.59 (t, *J*= 7.2 Hz, 2H), 7.92 (d, *J*= 8.0 Hz, 2H). Anal Calc. for $C_{25}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.18; H, 3.37.

3,3'-((2-chlorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 8)*: Off white solid; m.p. = 225-227 ˚C; FT-IR: ν_{max} (KBr): 3429, 1658, 1612, 1562, 1495, 1053, 759 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.16 (s, 1H), 7.16-7.23 (m, 2H), 7.27-7.37 (m, 6H), 7.56 (t, *J*= 7.6 Hz), 7.89 (d, *J*= 8.0 Hz). Anal Calc. for $C_{25}H_{15}ClO_6$: C, 67.20; H, 3.38. Found: C, 67.19; H, 3.32.

3,3'-((4-fluorophenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 9)*: Off white solid; m.p. = 213-215 ˚C; FT-IR: ν_{max} (KBr): 3424, 1670, 1610, 1561, 1501, 1099 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6): δ= 6.36 (s, 1H), 7.05 (t, *J*= 8.0 Hz, 2H), 7.19-7.29 (m, 2H), 7.31 (t, *J*= 8.8 Hz, 2H), 7.37 (d, *J*= 8.0 Hz, 2H), 7.59 (td, *J*= 8.4 , 2.0 Hz, 2H), 7.91 (dd, *J*= 8.0, 2.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 35.5, 104.3, 115.0,

116.1, 117.7, 124.0, 128.8, 132.2, 132.8, 135.7, 152.3, 159.5, 161.9, 165.1. Anal Calc. for $C_{25}H_{15}FO_6$: C, 69.77; H, 3.51. Found: C, 69.78; H, 3.48.

3,3'-((3-hydroxyphenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 10)*: Off white solid; m.p. = 256-258 ˚C; FT-IR: ν_{max} (KBr): 3397, 1655, 1612, 1569, 1489, 1054 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ= 6.28 (s, 1H), 6.52-6.58 (m, 3H), 7.0 (t, *J*= 8.0 Hz, 2H), 7.30-7.37 (m, 4H), 7.59 (t, *J*= 8.0 Hz, 2H), 7.91 (d, *J*= 8.0 Hz, 2H). Anal Calc. for $C_{25}H_{16}O_7$: C, 70.09; H, 3.76. Found: C, 70.08; H, 3.78.

3,3'-((2-hydroxyphenyl)methylene)bis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 11)*: Off white solid; m.p. = 258-260 ˚C; FT-IR: ν_{max} (KBr): 3251, 3078, 1710, 1671, 1634, 1571, 1220 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ= 5.74 (s, 1H), 7.14 (t, *J*= 7.8 Hz, 1H), 7.19 (d, *J*= 8.0 Hz, 1H), 7.31-7.45 (m, 5H), 7.43 (d, *J*= 8.4 Hz, 1H), 7.48 (d, *J*= 8.0 Hz, 1H), 7.59 (t, *J*= 8.0 Hz, 1H), 7.69 (t, *J*= 7.4 Hz, 1H), 8.07 (s, 1H), 8.08 (d, *J*= 7.6, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 28.7, 113.8, 116.1, 116.3, 116.5, 122.7, 124.0, 124.6, 125.4, 128.7, 132.3, 132.6, 149.2, 152.0, 156.3, 160.5. Anal Calc. for $C_{25}H_{16}O_7$: C, 70.09; H, 3.76. Found: C, 70.11; H, 3.74.

3,3',3'',3''',3'''',3'''''-((((1,3,5-triazine-2,4,6-triyl)tris (oxy))tris(3-methoxybenzene-4,1-diyl))tris (methane triyl))hexakis(4-hydroxy-2H-chromen-2-one) *(Table 2, Entry 12)*: Off white solid; m.p. = 284-286˚C; FT-IR: ν_{max} (KBr): 1712, 1652, 1618, 1357, 1263, 1217 cm^{-1},^1H NMR (400 MHz, DMSO-d_6): δ= 8.22-8.41 (m, 4H), 8.14-8.03 (m, 4H), 7.72 (t, 4H, *J*= 7.6 Hz), 7.59 (d, 4H, *J*= 8.2, 2.4 Hz), 7.50 (dd, 3H, *J*= 7.8, 2.2 Hz), 7.45 (d, 3H, *J*= 7.8 Hz), 7.34 (d, 3H, *J*= 2.2 Hz), 5.78 (s, 3H), 3.29 (s, 9H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ= 169.7, 163.5, 157.6, 154.6, 152.3, 147.6, 136.4, 133.4, 129.5, 127.4, 125.3, 124.2, 123.4, 121.5, 118.5, 113.2, 59.4, 31.9. Anal Calc. for $C_{81}H_{51}N_3O_{24}$: C, 67.08; H, 3.54; N, 2.90. Found: C, 67.05; H, 3.57; N, 2.88.

4. Conclusion

In conclusion, the POImD was investigated as a mild and efficient catalyst for the synthesis of substituted bis coumarin compounds. The remarkable advantages offered by this method are: the catalyst is non-toxic, inexpensive and reusable. Simple work-up procedure, short reaction time, high yields of product with better purity and green aspect by avoiding toxic catalyst and hazardous solvent are another benefits of this procedure. To the best of our knowledge this is the first report on synthesis of bis coumarin compounds using POImD.

Acknowledgements

Financial support by Rasht Branch, Islamic Azad University and Payame Noor University is gratefully acknowledged.

References

[1] F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Current Med. Chem.*, 12 (2005) 887-916.

[2] C. X. Su, J. F. Mouscadet, C. C. Chiang, H. J. Tsai and L. Y. Hsu, HIV-1 integrase inhibition of biscoumarin analogues. *Chem. Pharm. Bull.*, 54 (2006) 682-686.

[3] A. Lacy and R. O'Kennedy, Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. *Current Pharm. Design*., 10 (2004) 3797-3811.

[4] M. I. Choudhary, N. Fatima, K. M. Khan, S. Jalil, S. Iqbal and Atta-ur-Rahman, New biscoumarin derivatives-cytotoxicity and enzyme inhibitory activities. *Bioorg. Med. Chem*., 14 (2006) 8066-8072.

[5] U. M. Lindstrom, Stereoselective organic reactions in water. *Chem. Rev*. 102 (2002) 2751-2772.

[6] Z. B. Xu and J. Qu, Hot Water- Promoted SN1 Solvolysis Reactions of Allylic and Benzylic Alcohols. *Chem. Euro. J.* 19 (2013) 314-323.

[7] S. Chitra, N. Paul, S. Muthusubramanian and P. Manisankar, A facile, water mediated, microwave-assisted synthesis of 4,6-diaryl-2,3,3a,4-tetrahydro-1H-pyrido[3,2,1-jk]carbazoles by a domino Fischer indole reaction–intramolecular cyclization sequence. *Green Chem*. 13 (2011) 2777-2785.

[8] M. K. Mohammadi, S. J. Saghanezhad and N. Razzaghi-asl, Efficient and convenient oxidation of benzyl halides to carbonyl compounds with Sodium nitrate and Acetic acid by phase transfer catalysis in aqueous media. *Bull. Chem. Soc. Ethiop*., 31 (2017) 535-544.

[9] M. Nikpassand, L. Zare Fekri, Z. Gharib and Z. Jafarian, Potassium 2-oxoimidazolidine-1,3-diide as a novel catalystfor grind synthesis of pyrano[4,3- *b*]chromenone. *J. Chilean Chem. Soc.*, 63 (2018) 4195-4199.

[10] M. Nikpassand, L. Zare Fekri and A. Pourahmad, One-pot Synthesis of new azo-linked 4H-benzo [d][1, 3] oxazine-2, 4-diones from carbon dioxide using CuO@ RHA/MCM-41 nanocomposite in green media. *J. CO_2 Util.*, 27 (2018) 320-325.

[11] M. Nikpassand, L. Zare, M. Saberi, Ultrasound-assisted l-proline catalyzed synthesis of novel derivatives of azo-linked dihydropyridines. *Monatsh. Chem.* 143 (2012) 289-293.

[12] M. Nikpassand, L. Zare Fekri, L. Karimian and M. Rassa, Synthesis of biscoumarin derivatives using nanoparticle Fe_3O_4 as an efficient reusable heterogeneous catalyst in aqueous media and their antimicrobial activity. *Curr. Org. Synth.*, 12 (2015) 358-362.

[13] M. Nikpassand, L. Zare Fekri and P. Farokhian, An efficient and green synthesis of novel benzoxazole under ultrasound irradiation. *Ultrason. Sonochem.*, 28 (2016) 341-345.

[14] L. Zare Fekri, M. Nikpassand and R. Maleki, 1, 4-Diazabicyclo [2.2. 2] octanium diacetate: As an effective, new and reusable catalyst for the synthesis of benzo [d] imidazole. *J. Mol. Liq.,* 222 (2016) 77-81.

[15] V. Padalkar, K. Phatangare, S. Takale, R. Pisal and A. Chaskar, Silica supported sodium hydrogen sulfate and Indion 190 resin: An efficient and heterogeneous catalysts for facile synthesis of bis-(4-hydroxycoumarin-3-yl) methanes. *J. Saudi Chem. Soc.*, 19 (2015) 42-45.

[16] J. M. Khurana and S. Kumar, Ionic liquid: an efficient and recyclable medium for the synthesis of

octahydroquinazolinone and biscoumarin derivatives. Monatsh. *Chem.*, 141 (2010) 561-564.

[17] U. N. Yadav and G. S. Shankarling, Room temperature ionic liquid choline chloride–oxalic acid: A versatile catalyst for acid-catalyzed transformation in organic reactions. *J. Mol. Liq.,* 191 (2014) 137-141.

[18] M. A. Zolfigol, A. R. Mousavi-Zare and M. Zarei, Friedel–Crafts alkylation of 4-hydroxycoumarin catalyzed by sulfonic-acid-functionalized pyridinium chloride as a new ionic liquid. *Comptes Rendus Chimie.,* 17 (2014) 1264-1267.

[19] H. Kiyani, F. Ghorbani, Potassium phthalimide-catalysed one-pot multi-component reaction for efficient synthesis of amino-benzochromenes in aqueous media. *Chemical Papers,* 68 (2014) 1104-1112.

[20] K. Tabatabaeian, H. Heidari, A. Khorshidi, M. Mamaghani and N.O. Mahmoodi, Synthesis of biscoumarin derivatives by the reaction of aldehydes and 4-hydroxycoumarin using ruthenium (III) chloride hydrate as a versatile homogeneous catalyst. *J. Serb. Chem. Soc.*, 77 (2012) 407-413.

N. Tavakoli-Hoseini, M. M. Heravi, F. F. Bamoharram, A. Davoodnia and M. Ghassemzadeh, An unexpected tetracyclic product isolated during the synthesis of biscoumarins catalyzed by $[MIM(CH_2)_4SO_3H][HSO_4]$: Characterization and X-ray crystal structure of 7-(2-hydroxy-4-oxo-4H-chromen-3-yl)-6H,7H-chromeno[4,3-b]chromen-6-one. *J. Mol. Liq*.,

References

[1]. D. Chaudhuri, A.C. Roy, B. Biswas, et al. *Salmonella typhimurium* infection leads to colonization of the mouse brain and is not completely cured with antibiotics. *Front Microbiol* 2018; 9: 1632. doi: 10.3389/fmicb.2018.01632

[2] S.E. Majowicz, J. Musto, E. Scallan, F.J. Angulo, M. Kirk, S.J. O'Brien et al. International collaboration on enteric disease "Burden of Illness "studies. The global burden of non typhoidal *Salmonella* gastroenteritis. Clin. Infect.Dis. Off. Publ. Infect. Dis. Soc. Am. 50 (2010), 882-889. Doi:10.1086/650733

[3] B.K. Mandal, J. Brennand. Bacteremia in Salmonellosis; a 15 year retrospective study from regional infectious diseases unit. Br.Med.J. 297 (1998):1242-1243.

[4] A. Marzel, P.T. Desai, I. Nissan, Y.I. Schorr, J. Suez, L. Valinsky, et al. Integrative analysis of salmonellosis in Israel,1995–2012 reveals association of serovar 9,12:l,v:with extra intestinal infections,dissemination ofendemic *S.* Typhimurium DT104 bio types and a severe under-reporting of outbreaks. J.Clin.Microbiol. 52(2014) : 2078-2088.

[5] J.A. Crump, R.S. Heyderman. A perspective on invasive Salmonella disease in Africa. Clin Infect Dis. (2015); 61(Suppl 4):S235–40. doi:10.1093/cid/civ709.

[6] N.A. Feasey, G. Dougan, R.A. Kingsley, R.S. Heyderman, M.A. Gordon MA. Invasive non-typhoidal salmonella diseases: an emerging and neglected tropical diseases in Africa. Lancet 379 (2012): 2489-2499. doi: 10.1016/S0140- 6736(11)61752-2

[7] Maclennan CA (2014). Out of Africa: links between invasive non-typhoidal disease, typhoid fever and malaria. Clin. Infect.Dis. Off. Publ. Infect. Dis. Soc. Am. 58 (2007), 648-650. doi: 10.1093/cid/cit803

[8] I.V. Uche , C.A. MacLennan, A. Saul, S. Baker. A systematic review of the incidence, risk factors and case fatality rates of Invasive Nontyphoidal Salmonella (iNTS) disease in Africa (1966 to 2014). PLoS Negl Trop Dis. (2017);11(1):e0005118. doi:10.1371/journal.pntd.0005118.

[9] S.E Majowicz, J. Musto, E. Scallan, F.J. Angulo, M. Kirk, S.J. O'Brien, T.F. Jones, A. Fazil, R.M. Hoekstra. The global burden of nontyphoidal Salmonella gastroenteritis. Clin Infect Dis. (2010); 50(6):882– 889. doi:10.1086/650733.

[10] S.E.Park, G.D. Pak, P. Aaby, Y. Adu-Sarkodie, M. Ali, A. Aseffa, H.M. Biggs, M. Bjerregaard-Andersen, R.F. Breiman, J.A. Crump, et al. The relationship between invasive nontyphoidal Salmonella disease, other bacterial bloodstream infections, and malaria in Sub-Saharan Africa. Clin Infect Dis. (2016);62(Suppl 1):S23–31. doi:10.1093/cid/civ893.

[11] T.T. Ao, D.M. Daugla, J. Toralta, C. Ngadoua, F. Fermon, A.L. Page A-L, et al. Global burden of invasive nontyphoidal Salmonella disease, 2010(1). Emerg Infect Dis. (2015);21(6). doi:10.3201/eid2101.140256.

[12] J.A. Crump, F.M. Medalla, K.W. Joyce, A.L. Krueger, R.M. Hoekstra, J.M. Whichard, E.J. Barzilay. Antimicrobial resistance among invasive nontyphoidal *Salmonella enterica* isolates in the United States: national antimicrobial resistance monitoring system, 1996 to 2007. Antimicrob. Agents Chemother. 55 (2011):1148–1154.

[13] T. Grein, D. O'Flanagan, T. McCarthy, D. Bauer D. An outbreak of multidrug-resistant Salmonella typhimurium food poisoning at a wedding reception. *Ir. Med. J.*, 92 (1999), 238-241.

[14] M. Helms, S. Ethelberg, K. Molbak. International *Salmonella* Typhimurium DT104 infections, 1992–2001. Emerging Infectious Diseases. 11 (2005):859–867.

[15] S. Meakins, I.S. Fisher, C. Berghold, et al. Antimicrobial drug resistance in human nontyphoidal *Salmonella* isolates in Europe 2000–2004: a report from the Enter-net International Surveillance Network. Microbial Drug Resistance (Larchmont, NY). 14 (2008):31–35.

[16] C.A. Scherer, S.I. Miller. Molecular pathogenesis of salmonellae. In: Groisman EA (ed.) Principles of bacterial pathogenesis. Academic, New York (2001).

[17] A. Zapun, C. Contreras-Martel, T. Vernet. Penicillin-binding proteins and betalactam resistance. FEMS Microbiol. Rev. (2008); 32, 361–385.

[18] J.L. Mainardi, J.E. Hugonnet, L. Gutmann, M. Arthur. Fighting resistant tuberculosis with old compounds: the carbapenem paradigm. Clin. Microbiol. Infect. (2011); 17, 1755–1756

[19] Y. Chen, W. Zhang, Q. Shi, D. Hesek, M. Lee, S. Mobashery, B.K. Shoichet. Crystal structure of penicillin binding protein 6 from E.coli. J Am Chem Soc., 131 (2009): 14345-14354, doi: 10.1021/ja903773f

[20] F.E. Kerff, T. Mohammed, A. Juan, P. Ayala, C. Ayala. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis FEMS Microbiol Rev 32 (2008), 234–258.

[21] S.K.M. Jasmine, S.R.G. Vidya, N. Gorityala, S.R. Sagurthi, S. Mungapati, K.N. Manikanta,U.S. Allam. In Silico Modeling and Docking Analysis of CTX-M-5, Cefotaxime-Hydrolyzing β-Lactamase from

Human-Associated *Salmonella* Typhimurium. Journal of Pharmacology and Pharmacotherapeutics, (2022); 1–13, DOI: 10.1177/0976500X221109721

[22] S. Gnanendra, S. Mohamed, J. Natarajan J. Identification of potent inhibitors for *salmonella typhimurium* quorum sensing *via* virtual screening and pharmacophore modeling. Combinatorial Chemistry & High Throughput Screening. (2013); 6 (10): 1-14

[23] A. Beheshti, E. Pourbasheer, M. Nekoei, S. Vahdani S. QSAR modeling of antimalarial activity of urea derivatives using genetic algorithm–multiple linear regressions. J Saudi Chem Soc 20 (2016):282–290

[24] S. Shapiro, B. Guggenheim. Inhibition of oral bacteria by phenolic compounds. Part 1. QSAR analysis using molecular connectivity. *Quant. Struct. -Act. Relat.*17 (1998): 327–337.

[25] O. Trott, A.J. Olson. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry, 31 (2010): 455-461. DOI 10.1002/jcc.21334

[26] Y. Chen, W. Zhang, Q. Shi, D. Hesek, M. Lee, S. Mobashery, B.K. Shoichet. Crystal structure of penicillin binding protein 6 from E.coli. J Am Chem Soc., 131 (2009): 14345-14354, doi: 10.1021/ja903773f

[27] A. Daina, O. Michielin, V. Zoete. SwissADME: a free web tool to evaluate pharmacokinetics, druglikeness and medicinal chemistry friendliness of small molecules. SCientifiC REpOrtS; 2017,| 7:42717 | DOI: 10.1038/srep42717

[28] Lipinski CA. Lead and drug-like compounds: the rule of five revolution. Drug discovery today: Technologies. 2004; 1 (4): 337-341. Doi:10.1016/j.ddtec.2004.11.007

[29] P.R. Ortiz de Montellano. Cytochrome P450-activated prodrugs. Future Med Chem. 5(2013):213-228

[30] Gramatica P. On the development and validation of QSAR models. Methods Mol Biol. 2013; 930:499-526. doi: 10.1007/978-1-62703-059-5_21

[31] Roy K, Das RN, Ambure P, Aher RB. Be aware of error measures. Further studies on validation of predictive QSAR models *Chemometr*. *Intell. Lab. Syst.*, 2016; *152*, 18–33.

[32] M. Jalali-Heravi, A. Kyani. Use of computerassisted methods for the modeling of the retention time of a variety of volatile organic compounds: A PCA-MLR-ANN approach. J. Chem. Inf. Comput. Sci., 4 (2004):1328–1335

[33] J.P. Ameji, I.S. Muhammad, S.R. Akinleye, G.A. Okorn, W.I. Aderemi. International Journal of Biochemistry, Biophysics & Molecular Biology. 2(2017): 36-46. doi: 10.11648/j.ijbbmb.20170205.11

[34] H. Rafidi, S. Rajan, K. Urban, W. Shatz-Binder, K. Hui, Z.G. Ferl, et al. Effect of molecular size on interstitial pharmacokinetics and tissue catabolism of antibodies. mAbs, 14 (2022), https://doi.org/10.1080/19420862.2022.2085535

[35] R.L. Slaughter, D.J. Edwards. Recent advances: the cytochrome P450 enzymes. Ann Pharmacother, 29 (1995):619-24.

[36] M.P. Doogue, T.M Polasek. The ABCD of clinical pharmacokinetics. Ther Adv Drug Saf. 4(2013):5-7

[37] T. Lynch, A. Price. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. Am Fam Physician 2007; 76:391-6.

[38] P.R. Ortiz de Montellano. Cytochrome P450-activated prodrugs. Future Med Chem. 5(2013):213-228

[39] J.B. Sakai. Pharmacokinetics: The Absorption, Distribution, and Excretion of Drugs. In: Practical Pharmacology for the Pharmacy Technician. Jones and Bartlett Publishers,ISBN 139780781773485 (2009).