Current Chemistry Letters 14 (2025) 129–138

Contents lists available at GrowingScience

Current Chemistry Letters

homepage: www.GrowingScience.com

PEG 400-Catalyzed *C3 &O*-Alkylation Reactions of 4-Hydroxycoumarin-A Study

Madhuri Pulagam[a] and Hari Babu Bollikolla[a,b]*

[a]*Department of Chemistry, Acharya Nagarjuna University, N Nagar-522 510, Andhra Pradesh, India*
[b]*Department of Chemistry, Andhra Kesari University-523 001, Ongole, Andhra Pradesh, India*

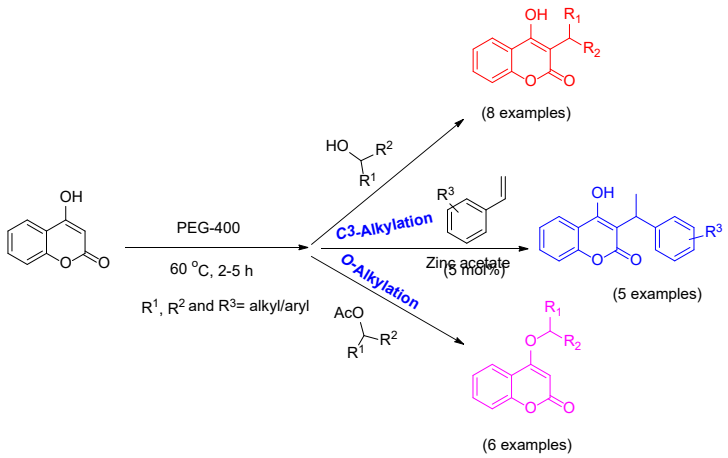
C H R O N I C L E

Article history:
Received February20, 2024
Received in revised form
May3, 2024
Accepted August19, 2024
Available online
August19, 2024

Keywords:
C-H Functionalization
C-C and C-O bond formations
PEG-400
4-hydroxy coumarin
Secondary benzyl alcohol
Secondary benzyl O-acetate
Styrenes and recyclability

A B S T R A C T

PEG-400 has been found to be an efficient recyclable catalyst/solvent system for *C3*- and *O*-alkylation of 4-hydroxycoumarin with a variety of electronically and structurally divergent alcohols with moderate to good yield of products. The *C3*-alkylation of styrenes requires $Zn(OAc)_2.2H_2O$ (5 mol%) in PEG-400 at 70 °C. PEG-400 was used at 60 °C to *O*-alkylate 4-hydroxycoumarin with acetates. This procedure also provided a gentle and simple method for obtaining multi-substituted pyranocoumarins. This protocol's advantage include its widespread use, mild environmental impact , low cost, reusable catalyst (PEG-400), and convenience of use due to the only byproducts being acetic acid and water, respectively.



Graphical Abstract

1. Introduction

In addition to their use as functional materials,[1-2] coumarins are a preferred scaffold among heterocycles and are known to have a variety of biological activities, such as antibacterial, antiviral, antifungal, and cytotoxic properties.[3-9] Particularly,

* Corresponding author
E-mail address dr.b.haribabu@gmail.com(Bollikolla)

doi: 10.5267/j.ccl.2024.8.004

the 4-hydroxycoumarins and their 3-alkylated derivatives have generated a lot of interest because they work as nonpeptide HIV protease inhibitors and as "anticoagulant rodenticides as well as antithrombotic agents," including warfarin, brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen (**Fig 1**).[10-12] The synthesis of new C-C and C-O bonds through C-H functionalization, also known as *C3* or *O*-alkylation of 4-hydroxycoumarin, is arguably one of the most significant and difficult reactions in synthetic chemistry because of its potential applications in medicine. It can also be used to create a variety of 3,4-substituted compounds.[13-14] Despite the fact that there are numerous studies on the C3-alkylation of 4-hydroxycoumarins, the most of them require organic halides or boronic acid as substrates for base-mediated alkylation reactions or Pd-catalyzed C-C bond formation.[15-16] Because starting materials are easily obtained and the only byproduct produced is water, alcohols are a more appealing source from a synthetic perspective than comparable halides or boronic acid. It has not been well investigated, but an alternative method of alkylation using alcohols as alkylating agents can be carried out in an acidic environment. Strong acids like HCl, H_2SO_4, $Yb(OTf)_3$, $FeCl_3.6H_2O$, Amberlite IR-120, molecular iodine, $Bi(OTf)_3$, $Fe(ClO_4)_3.xH_2O$, TMSOTf, $Bi(NO_3)_3.5H_2O$/Ionic liquid system, Ir-Sn bimetallic system, sulfated tin oxide, and zinc acetate are among the methodologies for the *C3*-alkylation of 4-hydroxy coumarin with alcohols that have been reported thus far.[17-19] However, procedures utilizing traditional acids are always linked to issues such high toxicity, corrosion, waste from catalysts, and challenges with recovery and separation. Some of these catalytic systems are limited by lengthier reaction times, a lack of reusability, low yields, and the use of toxic solvents or reagents. Thus, it is more crucial and ideal to create a novel, effective catalytic technique for the direct *C3*-alkylation of4-hydroxycoumarin employing alcohols. Utilizing atom-efficient catalytic processes in the production of fine chemicals and pharmaceuticals has garnered interest due to the growing recognition of the urgent need for greener, more sustainable technology. The use of substitute reaction media, which avoids the issues with many of the conventional volatile organic solvents, is one such element that is gaining more and more attention. Many environmentally friendly, compatible alternative reaction media have been investigated over time, including polyethylene glycol, ionic liquids, and supercritical fluids.[20-21] From this angle, polyethylene glycol (PEG) serves as a green solvent and substitute reaction media.[22-25] For over twenty years, PEG has been investigated as a solvent for chemical synthesis. A reassessment of early work was conducted in 2005.[26-27] PEG's biodegradable, biocompatible, non-toxic, and benign qualities make it a popular choice in organic synthesis over harmful organic solvents. PEG has allegedly been utilised as a solvent in a number of heterocyclic molecule synthesis reactions, oxidations and reductions, heteroatom-heteroatom bond-forming reactions, and carbon-carbon and heteroatom-heteroatom bond-forming reactions.[28-36]

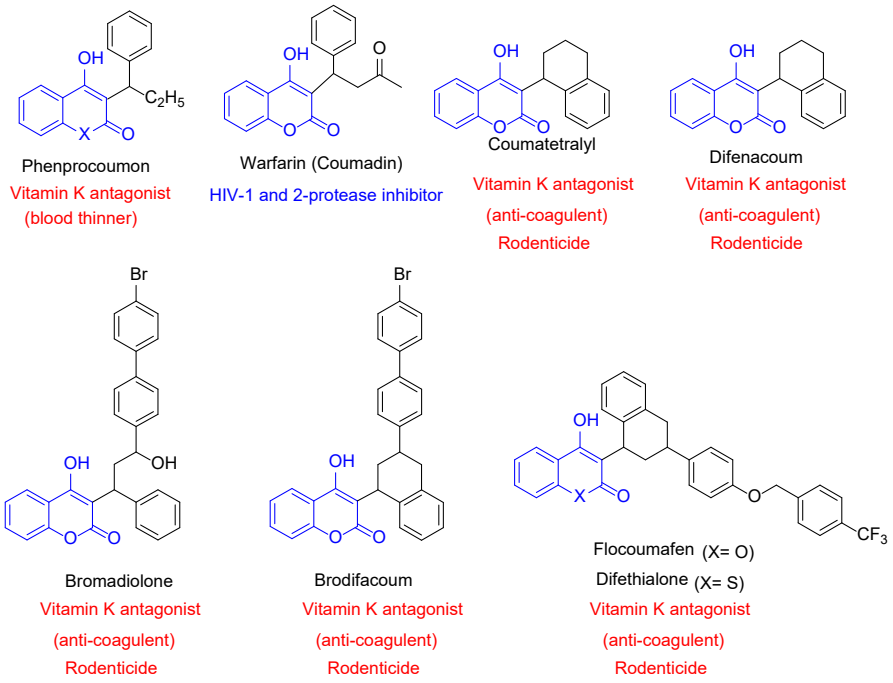


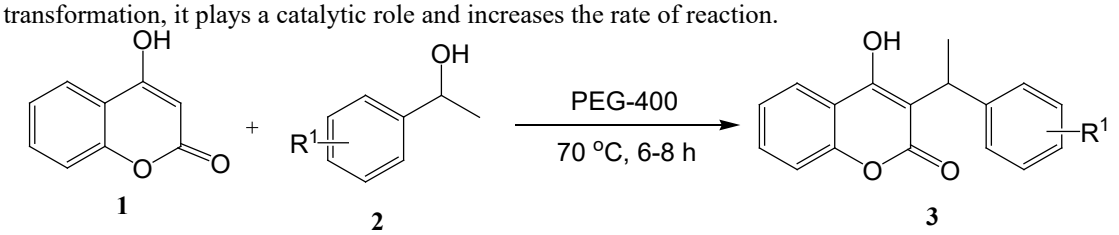
Fig. 1. Representative 4-hydroxycoumarins in market

We have successfully used PEG-400 as an effective catalyst and solvent solution for the title work in this study, which is a continuation of our research on investigating novel synthetic techniques for C-H functionalization[30,37-42] herein. The results are reported here.

2. Results and Discussion

As a model reaction, we first looked into the various reaction conditions for the three-component reaction involving 4-hydroxycoumarin (**1**, 4-HC, 1 mmol) and1-phenylethanol (**2a**, 1.1 mmol). **Table 1** summarizes the findings of an investigation into the impact of temperature and solvent on the synthesis of the desired product, 4-hydroxy-3-(1-

phenylethyl)-2*H*-chromen-2-one (**3a**). Even after a considerable period of time (24 h, Table 1, entry 1), the reaction did not continue in solvent-free conditions. The rate of the reaction might be affected by the reactants' solubility. We looked at a variety of solvent types at various temperatures, including polar-aprotic (DMF, CH_3CN, and THF), non-polar (toluene), and polar-protic (H_2O, MeOH, EtOH, and PEG-400) (**Table 1**, entries 2-13). In both polar and non-polar aprotic solvents, the process was stopped (**Table 1**, entries 2-4). The reaction proceeded in solvents H_2O, MeOH, and EtOH, providing yields of the intended product **3** of 0%, 17%, and 21%, respectively (**Table 1**, entries 5-7). It's interesting to note that using PEG-400 as the solvent resulted in a much higher yield (75%) of product 3 in a shorter reaction period (6 h) (**Table 1**, entry 12). Regarding the product yield and reaction rate, PEG-400 outperformed all other investigated solvents for the reaction under test. Due to its moderate acidity, PEG has become the most used phase transfer catalyst. In order to accomplish the intended product transformation, it plays a catalytic role and increases the rate of reaction.



1 **2** **3**

Table1. Screening for the reaction conditions[a]

Entry	Solvent	Temp (^oC)	Time (h)	Yield[b] (%)
1	Neat	70	24	NR
2	THF	70	8	NR
3	Toluene	70	8	NR
4	DMF	70	8	NR
5	CH_3CN	70	8	NR
4	*n*-hexane	70	6	NR
5	H_2O	70	6	NR
6	MeOH	70	5	17
7	ETOH	70	5	21
8	PEG-400	25	12	28
9	PEG-400	40	8	32
10	PEG-400	50	8	40
11	PEG-400	60	8	58
12	**PEG-400**	**70**	**6**	75
13	PEG-400	80	6	75

[a]1.0 mmol**1a,** 1.2 mmol **2b** in 5 mL PEG; [b] Isolated yield [NR = No reaction]

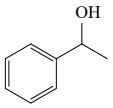
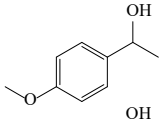
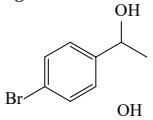
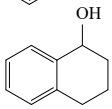
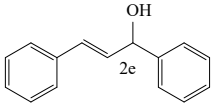
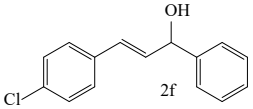
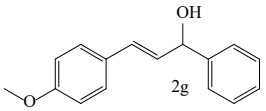
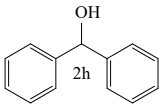
Additionally, the reaction at ambient temperature recorded 28% of the product yield for 12 hours after screening the process at various reaction temperatures using PEG-400 as a solvent (**Table 1**, entry 8). It's interesting to note that at 40 °C, 50 °C, and 60 °C, respectively, there was a higher product yield (32%, 40%, and 58%) and a decreased reaction time (8 h) (**Table 1**, entries 9-11). The reaction gave the maximum yield (75%) of the product **3a** in a 6-hour reaction time when the temperature rose from 60 °C to 70 °C (**Table 1**, entry 12). The yield (75%) at 70 °C did not improve any more (**Table 1**, item 13). As a result, we determined that the optimal temperature for the model reaction was 70 °C. The formation of desired product **3a** is established by mp, IR, NMR and mass spectral analyses. Disappearance of olefin proton of the starting material (4-HC) and OH group 1-phenylethanol and appearance of signal δ 111.1 of C3-carbon in ^{13}C NMR indicates *C3*-alkylation of 4-hydroxycoumarin with 1-phenylethanol. EI-MS of **3a** shows the molecular ion peak of 266. The R_f, t_R, mp and IR of the synthesized compound are in accordance with that of literature precedent.[18]

We subsequently assessed the extent of the benzylation of 4-hydroxycoumarin **1** using a range of structurally divergent reactants after obtaining the ideal reaction conditions (PEG-400 at 70 ^0C). The outcomes are listed in **Table 2**. In 68-81% yields, we were able to extract the equivalent *C3*-alkylated compounds (**3a-h**) after 5 hours (entry 1-3, Table 2). When benzylic alcohols contain electron-donating groups like methoxy, the process produced larger yields (entry 2, **Table 2**). The reaction did not occur at all when nitro groups containing benzylic alcohol were supplied in place of bromo- or methoxy groups. We were intrigued by these findings, so we modified the procedure to create an anticoagulant molecule, Coumatetralyl (**3d**, **Table 2**), utilizing 1,2,3,4-tetrahydro-1-napthanol (**2d**) and 4-hydroxycoumarin in 70% yield. Furthermore, we achieved exceptional yields when we carried out this reaction with substituted allylic alcohols (entries 5-7 and 9, Table 2). Using primary benzyl alcohols did not produce the desired result. The success of the direct *C3*-alkylation of 4-hydroxycoumarin was limited to secondary benzylic alcohols, as these results unequivocally show. Even after refluxing for 20 hours, the reaction between 2-hydroxycoumarin and benzhydrol did not continue (entry 8, **Table 2**).

Similarly, styrene (**4a**) was examined for its ability to react with 4-hydroxy coumarin (**1**) under optimal conditions based on a precedent report,[43] and interestingly, no direct *C3*-alkylation was seen, even after the reaction was allowed to proceed for a whole day. Using PEG-400 as the reaction medium, various Lewis acids (LAs), including $Zn(OAc)_2.2H_2O$, $ZnCl_2$, $FeCl_3$, CuBr, and $CuCl_2$, were screened. Thankfully, the reaction continued to produce the matching *C3*-alkylated product, **3a**. The disappearance of styrene olefinic protons clearly indicated the *C3*-alkylation of 4-hydroxycoumarin with styrene. Zinc acetate, despite being less expensive and readily available, turned out to be the best LA among those tested in terms of isolated yield and shorter reaction durations. Because of its unique physical and chemical characteristics, which show

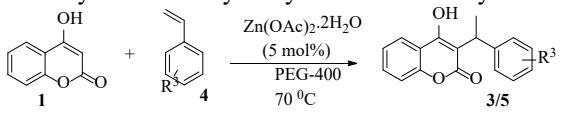
that it can be effective in enabling a broad range of synthetic transformations in both organic synthesis and catalysis, $Zn(OAc)_2.2H_2O$ is known as a multifunctional catalyst.[44-50] For the styrene addition, the ideal reaction conditions are $Zn(OAc)_2.2H_2O$ (5 mol%) in PEG-400 at 70 °C. Subsequently, functionalities of $-CH_3$, $-OCH_3$, -Br, and -Cl were investigated on electrically divergent styrenes (**4b-e**), and moderate to good yields were achieved (**3a-c**, **5a-b**, **Table 3**).

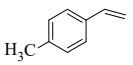
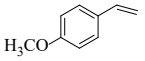
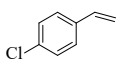
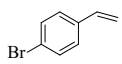
Table 2. *C3*-alkylation of 4-hydroxycoumarin with various alcohols

Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1	 2a	3a	6	75
2	 2b	3b	6	81
3	 2c	3c	6	83
4	 2d	3d	8	67
5	 2e	3e	8	74
6	 2f	3f	8	72
7	 2g	3g	8	85
8	 2h	3h	24	0

[a] Isolated yields after column chromatography.

Table 3. *C3*-alkylation of 4-hydroxycoumarin with styrenes

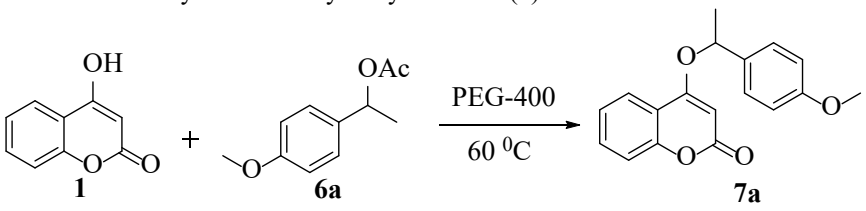


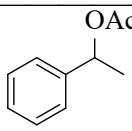
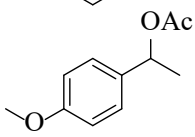
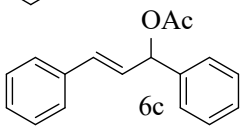
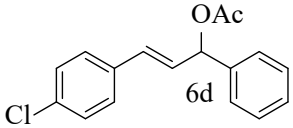
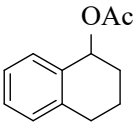
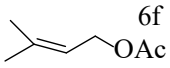
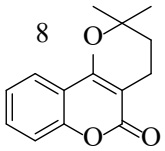
Entry	styrene	product	time (h)	yield (%)[a]
1		3a	4	81
2		5a	4.5	78
3		3b	4	85
4		5b	5.5	77
5		3c	6	71

[a]Isolated yields

We then focused on examining the viability of using secondary benzyl acetates (**6a-f**, prepared immediately for the purpose) to react with 4-hydroxycoumarin under the above optimized conditions to produce novel compounds (**7a-e**) with moderate to good yields (67-82%) in the allotted time after the successful direct *C3*-alkylation of 4-hydroxycoumarin with secondary benzyl alcohols and styrenes (new C-C bond formation) (**Table 4**). Using PEG-400 catalysis, this method is successfully applied to a new C-O bond forming process. As expected, rather than the anticipated *O*-alkylated product (**7f**), we extracted pyranocoumarin (**8**) in good yield when prenyl acetate (**6f**) interacted with 4-hydroxycoumarin (entry 6, Table 3) that is in accordance with the precedent literature reports. This process offers a gentle and uncomplicated way to obtain multi-substituted pyranocoumarins.[51-53]

Table 4. *O*-Alkylation of 4-hydroxycoumarin (**1**) with various acetates



Entry	Acetate	Product	Time (h)	Yield (%)a
1	 6a	7a	4	67
2	 6b	7b	4	78
3	 6c	7c	5	73
4	 6d	7d	5	70
5	 6e	7e	6	82
6	 6f	 8	5	65

a Isolated yields after column chromatography.
b Intramolecular cyclization.

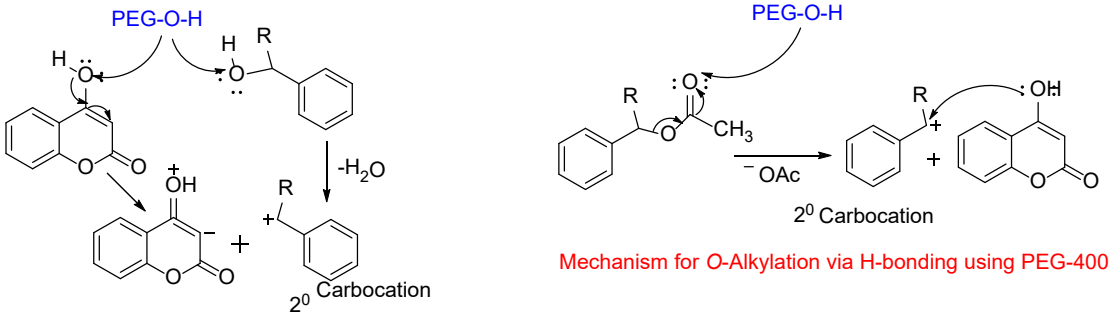


Fig.2. Proposed mechanism for the PEG-400 mediated *C3*-and *O*-alkylation

The reaction's suggested mechanism can be roughly seen as a series of tandem reactions, as shown in **Fig.2**, that remove water molecules as byproducts by creating stabilized carbocations, which function as the alkylating species. These carbocations are derived from alcohol (or, alternatively, from the formation of dimeric ether) in the presence of PEG-400-

using its Bronsted acidic site (*C3*-alkylation). PEG-O-H uses an H-bond to activate the enolic hydroxyl group, which increases the 3-position's nucleophilicity. On the other hand, in the instance of *O*-alkylation, PEG-O-H activates the carbonyl functionality of acetate by H-bonding, forming it as a leaving group. The stabilized carbocation that is thus generated subsequently interacts with enolic hydroxide to produce AcOH as a byproduct. One key question concerning sustainable chemistry is the recyclability of reagents. For the synthesis of product **3a** in PEG-400, the separation of the products and the reaction medium were investigated. The yield dropped from 75% to 58% after five runs, but we were happy to find out that the reaction medium could be successfully recycled for a maximum of five cycles with little loss of activity.

3. Conclusion

In conclusion, we have effectively used PEG-400 as an effective catalyst/solvent system to encourage the *C3*-benzylation of 4-hydroxycoumarin by employing secondary benzyl alcohols such as benzylic, and allylic alcohols and styrenes, as well as secondary benzyl acetates for *O*-alkylation. In total, 15 compounds were synthesized and all of them are known and compared their structures with the literature precedents. This protocol's benefits include its wide use, moderate environment, low cost, reusable catalyst (PEG-400, up to five cycles), and ease of usage due to the only byproducts being acetic acid and water, respectively. Additionally, this approach offers a gentle and uncomplicated way to obtain multi-substituted pyranocoumarins. The present developed green methodology can be handy for the researchers to exploit the applications of PEG-400 for the synthesis of biologically relevant heterocycles.

4. Experimental

Without undergoing additional purification, all chemicals were purchased from for-profit suppliers (TCI Chemicals Co. Ltd., Tokyo, Japan, and Alfa Aesar, Ward Hill, MA, USA). Merck Kieselgel 60 and F254 plates were used for TLC, while silica gel (60-120 mesh) was used for column chromatography with an ethyl acetate and hexane mixture as the eluent. Fisher John's melting point device was used to record melting points. Using a Perkin Elmer FTIR-240 C spectrophotometer, IR spectra were captured. Using a Bruker Avance 300 MHz spectrophotometer, ^{1}H and ^{13}C NMR spectra were captured. Regarding the internal TMS, chemical shifts are expressed in ppm, while *J* values are mentioned in Hz.

Standard experimental protocol for 4-hydroxycoumarin (alcohol) *C3*-alkylation (3a-h)
5-Hydroxycoumarin (**1**, 1.0 mmol) and secondary benzyl alcohol (**2a-h**, 1.1 mmol) in PEG-400 (5 mL) were combined, and the reaction mixture was left to stir at 70 °C for the specified amount of time (see to **Table 2**). Following the conclusion of the reaction, which was observed by thin-layer chromatography, the mixture was diluted with anhydrous diethyl ether and allowed to stir for fifteen minutes. Subsequently, the layers were allowed to separate and the ether layer was decanted. The mother liquor (PEG) was set aside for subsequent runs, and this procedure was performed twice to provide the crude products in diethyl ether. Following solvent evaporation, the crude product was refined using column chromatography on silica gel with 1:1 petroleum ether/ethyl acetate to produce the pure corresponding *C3*-alkylated products (**3a-h**).

4-Hydroxy-3-(1-phenylethyl)-2*H*-chromen-2-one (3a): White crystalline solid. mp: 204-205 ºC; Rf (*n*-Hexane:EtOAc, 1:1) = 0.4; IR (KBr): n~ = 3427 (s), 1672 (vs), 1626 (vs), 1393 (s), 1214 (s), 753 (s) cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.73 (d, *J* = 7.3 Hz, 3H, C<u>H</u>$_3$CH); 4.66 (q, 3 *J* = 7.3 Hz, 1H, CH$_3$C<u>H</u>); 7.14 (m, 1H, *p*-Ph); 7.25 (m, 2H, *m*-Ph); 7.29 (dd, *J* = 8.2 Hz, 1.0 Hz, 1H, H-8); 7.35 (ddd, *J*= 8.0 Hz, 7.3 Hz, 1.0 Hz, 1H, H-6); 7.41 (m, 2H, *o*Ph); 7.60 (ddd, J = 8.2 Hz, 7.3 Hz, 1.6 Hz, 1H, H-7); 8.00 (dd, *J*= 8.0 Hz, 1.6 Hz, 1H, H-5); ^{13}C NMR (100 MHz, acetone-d_6): δ = 17.2 (CH$_3$); 35.1 (C-9); 111.1 (C-3); 117.1(C-8); 117.2 (C-4a); 123.8 (C-5); 124.5 (C-6); 126.7 (*p*-Ph); 128.2 (*o*-Ph); 128.8 (*m*-Ph); 132.5 (C-7); 144.9 (*i*-Ph); 153.6 (C-8a); 160.0 (C-4); 162.1 (C-2); t_R = 25,72 min; MS (EI) *m/z* (%) = 266 (100) [M^+], 251 (67), 237 (4), 223 (33), 207 (10), 188 (7), 175 (51), 161 (6), 145 (20), 121 (35), 105 (39), 92 (10), 77 (11) [Ph^+].

Standard experimental protocol for 4-hydroxycoumarin (styrenes) *C3*-alkylation (5a-e)
For the duration given in **Table 3**, the reaction mixture containing 1-hydroxycoumarin **1a** (1 mmol), styrene **4a** (1 mmol), and Zn(OAc)$_2$.2H$_2$O (5 mol%) in PEG-400 (5 mL) was left to stir at 70 ºC. Following TLC completion, the reaction mixture was allowed to cool to room temperature before being diluted with water and 10 mL of ethyl acetate. The organic layer was then filtered after the mixture was dried over anhydrous Na_2SO_4. Following solvent evaporation, the crude product was refined using column chromatography on silica gel with 6% to 8% petroleum ether/ethyl acetate to produce the pure corresponding product (**5a-e**).

4-Hydroxy-3-(1-(*p*-tolyl)ethyl)-2*H*-chromen-2-one (5a):[431]^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.70-7.68 (m, 1H), 7.52-7.47 (m, 1H), 7.38 (d, *J* = 8 Hz, 2H), 7.30-7.27 (m, 1H), 7.24-7.20 (m, 3H), 6.45 (s, 1H), 4.72-4.66 (m, 1H), 2.35 (s, 3H), 1.65 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz):*δ* 163.7, 159.9, 152.6, 138.5, 137.7, 131.8, 130.5, 127.3, 123.9, 123.0, 116.4, 116.3, 110.2, 34.3, 21.1, 16.7.

Standard experimental protocol for 4-hydroxycoumarin *O*-alkylation (7a-e, 8)
4-Hydroxycoumarin (**1**, 1.0 mmol) and secondary *O*-acetyl compound (**6a-f**, 1.1 mmol) in PEG-400 (5 mL) were combined, and the reaction mixture was agitated at 60 ºC for the specified amount of time (see to **Table 4**). Water was added to the reaction mixture once the reaction (which was being watched over by TLC) was finished. After extracting in ethyl acetate, adjust pH neutral with sodium carbonate. After being dried over anhydrous Na_2SO_4, the organic phase evaporated under

vacuum. Using petroleum ether/ethyl acetate (1:3) as the eluent, the residue was purified using a silica gel column to provide the corresponding *O*-alkylated 4-hydroxycoumarin (**7a-e** and **8**).

4-(1-Phenylethoxy)-2*H*-chromen-2-one (**7a**).[18] Off white solid; mp: 214-218 °C. IR (KBr): ν 1669, 1621, 1492, 1401, 1218, 1168, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* =12.4 Hz, 1H), 7.64-7.43 (m, 5H), 7.64-7.42 (m, 2H), 7.23 (dd, *J* =10.8 Hz, 1H), 5.99 (s, 1H), 4.74 (q, *J*=9.6 Hz, 1H), 1.68 (d, *J*= 9.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 160.0, 152.6, 141.8, 132.1, 129.8, 127.7, 127.5, 123.9, 123.0, 116.3, 116.2, 110.3, 34.8, 16.8 ppm. MS (ESI): *m/z* (rel. abund. %) 267.3 ($[M+1]^+$, 100).

3,4-Dihydro-2,2-dimethylpyrano [3,2-*c*]chromen-5(2*H*)-one (**8**):[18] Semi solid. IR (KBr): 1721, 1636, 1614, 1497, 1451, 1383, 1276, 1203, 1171, 1118, 1016, 764, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (dd, *J* =10 Hz, 1H), 7.61-7.57 (m, 1H), 7.39-7.30 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 1.87 (t, *J* = 6.4 Hz, 2H) 1.47 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.03, 60.1, 150.3, 128.4, 125.5, 121.6, 117.4, 100, 78.2, 35.5, 27.7, 15.8 ppm. MS (ESI): *m/z* (rel. abund. %) 231.3 ($[M+1]^+$,100).

All compounds are known and their authenticity is compared to the literature reports.[18,19,43]

This work confirms that heterocyclic compounds are very important in different fields due to the high variety of their applications.[54-60]

Acknowledgement

Prof. HBB and Mrs. MP thank the Department of Chemistry, Acharya Nagarjuna University for constant support and BHB also thank DST, New Delhi for instrumental support through SERB-SURE MRP (SUR/2022/002273 dt. 25.09.2023).

References

[1] Safavi-Mirmahalleh S-A., Golshan M., Gheitarani B., Hosseini M. S., and Salami-Kalajahi M. (**2023**) A review on applications of coumarin and its derivatives in preparation of photo-responsive polymers. *Eur. Poly. J*., 198 112430. https://doi.org/10.1016/j.eurpolymj.2023.112430.

[2] Cao D., Liu Z., Verwilst P., Koo S., Jangjili P., Kim J. S., and LinW. **(2019)** Coumarin-based small-molecule fluorescent chemosensors. *Chem. Rev.*, 119(18), 10403-10519. https://doi.org/10.1021/acs.chemrev.9b00145.

[3] Citarella A., Vittorio, S., Dank, C., and Ielo L. (**2024**) Syntheses, reactivity, and biological applications of coumarins. *Front Chem*., 12 1362992. Doi: 10.3389/fchem.2024.1362992.

[4] Annunziata F., Pinna C., Dallavalle S., Tamborini L., and Pinto A. (**2020**) An overview of coumarin as a versatile and readily accessible scaffold with broad-ranging biological activities. *Int. J. Mol. Sci.,* 214618. https://doi.org/10.3390/ijms21134618.

[5] Srikrishna D., Godugu C., and Dubey P. K. (**2018**) A review on pharmacological properties of coumarins. *Mini Rev. Med. Chem.,* 18 113-141. 10.2174/1389557516666160801094919.

[6] Balewski Ł., Szulta S., Jalińska A., and Kornicka A. (**2021**) A mini-review: Recent advances in coumarin-metal complexes with biological properties. *Front. Chem*., 9781779. 10.3389/fchem.2021.781779.

[7] Srikrishna D., Godugu C., and Dubey P. K. (**2018**) A review on pharmacological properties of coumarins. *Mini Rev. Med. Chem.,* 18(2) 113-141. 10.2174/1389557516666160801094919.

[8] Bouhaoui A., Eddahmi M., Dib M., Khouili M., Aires A., Catto M.,&BouissaneL. (**2021**) Synthesis and biological properties of coumarin derivatives-A review. *ChemistrySelect,* 16(24) 5848-5870. https://doi.org/10.1002/slct.202101346.

[9] Gouda M. A., Salem M. A., and Helal M. H. (**2020**) A review on synthesis and pharmacological activity of coumarins and their analogs. *Curr. Bioactive Comp.,* 16(6) 818-836. https://doi.org/10.2174/1573407215666190405154406.

[10] Borah B., Dwivedi K. D., and Chowhan L. R. (**2021**) 4-Hydroxycoumarin: A versatile substrate for transition-metal-free multicomponent synthesis of bioactive heterocycles. *Asian J. Org. Chem.,* 10(12) 3101-3126. https://doi.org/10.1002/ajoc.202100550.

[11] Jung J-C., and Park O-S. (**2009**) Synthetic approaches and biological activities of 4-hydroxycoumarin derivatives. *Molecules.* 14(11) 4790-4803. 10.3390/molecules14114790.

[12] Romal J. R. A., and Ong S. K. (**2023**) Extending the library of 4-hydroxycoumarin derivatives with potential pharmacological activity by a catalyst-free and purification-free method. *ChemistrySelect,* 8(10) e202300519. https://doi.org/10.1002/slct.202300519.

[13] Ziarani G. M., Moradi R., Ahmadi T., and Gholamzadeh P. (**2019**) The molecular diversity scope of 4-hydroxycoumarin in the synthesis of heterocyclic compounds *via* multicomponent reactions. *Mol. Divers.,* 23 1029-1064. https://doi.org/10.1007/s11030-019-09918-7.

[14] Mali G., Maji S., Chavan K. A., Shukla M., Kumar M., Bhattacharyya S., andErandeR. D. (**2022**) Effective synthesis and biological evaluation of functionalized2,3-dihydrofuro[3,2-*c*]coumarins via an imidazole-catalyzed green multicomponent approach. *ACS Omega,* 7(40)36028-36036. https://doi.org/10.1021/acsomega.2c05361.

[15] Abdou M. M., El-Saeed R. A., and Bondock S. (**2019**) Recent advances in 4-hydroxycoumarin chemistry. Part 1: Synthesis and reactions, *Arabian J. Chem*., 12(1) 88-121. https://doi.org/10.1016/j.arabjc.2015.06.012.

[16] Abdou M. M., El-Saeed R. A., and Bondock S. (**2019**) Recent advances in 4-hydroxycoumarin chemistry. Part 2: Synthesis and reactions, *Arabian J. Chem*., 12(7) 974-1003. https://doi.org/10.1016/j.arabjc.2015.06.029.

[17] Su Q., Qian H., Li Z., Sun X., and Wang Z. (**2017**) Lewis-base-catalyzed alkylation reaction of 4-hydroxycoumarins with allenoates: Regioselective synthesis of 2*H*-[3,2-*c*] furocoumarins and 4-hydroxycoumarin vinyl ether derivatives. *Asian J. Org. Chem.,* 6(5) 512-515. https://doi.org/10.1002/ajoc.201600631.

[18] Narayana V., Varala R., and Zubaidha P. K. (**2012**) SO_4^{2-}/SnO_2-Catalyzed C3-alkylation of 4- hydroxycoumarin with secondary benzyl alcohols and *O*-alkylation with *O*- acetyl compounds. *Int. J. Org. Chem.*, 2 (3A) 287-294. 10.4236/ijoc.2012.223039

[19] Bandaru S. K., and Risi M. C. (**2022**) $Zn(OAc)_2.2H_2O$-Catalyzed C3-alkylation and *O*-alkylation of 4-hydroxycoumarin derivatives. *Caribbean J. Sci. Tech.*, 10(2) 10-16.10.55434/CBI.2022.2010 and references cited therein.

[20] Winterton N. (**2021**) The green solvent: a critical perspective. *Clean Technol. Environ. Policy.,* 23(9) 2499-2522. 10.1007/s10098-021-02188-8.

[21] Sheldon R. A. (**2005**) Green solvents for sustainable organic synthesis: state of the art. *Green Chem.,* 7267-278. https://doi.org/10.1039/B418069K

[22] Soni J. P., Nusrat S., Sethiya A., and Agarwal S. **(2020**) Polyethylene glycol: A promising approach for sustainable organic synthesis. *J. Mol. Liq.,* 315, 113766. https://doi.org/10.1016/j.molliq.2020.113766

[23] Hoffmann M. M. Polyethylene glycol as a green chemical solvent. (**2022**) *Curr. Opin. Colloid In.,* 57 101537. https://doi.org/10.1016/j.cocis.2021.101537

[24] Liwei X., Fucai D., Zheng L., Xuemin J., Jie K., and Guangxian L. (**2019**)Polyethylene glycol: A new medium for green organic synthesis[J]. *Chin. J. Org. Chem*., 39(3) 648-660.https://doi.org/10.6023/cjoc201807056

[25] Kardooni R., and Kiasat A. R. (**2020**) Polyethylene glycol as a green and biocompatible reaction media for the catalyst free synthesis of organic compounds.*Curr. Org. Chem*., 24 1275-1314. 10.2174/1385272824999200605161840

[26] Chen J., Spear S. K., Huddleston J. G., and Rogers R. D. (**2005**) Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chem*., 7 64-82. https://doi.org/10.1039/B413546F

[27] Andrade C. K. Z., and Alves L. M. (**2005**) Environmentally benign solvents in organic synthesis: current topics. *Curr. Org. Chem.,* 9 195-218. https://doi.org/10.2174/1385272053369178

[28] Qadir M., Yaseen A., and Shah W. A. (**2023**) PEG-400 catalysed selective C-Se cross dehydrogenative coupling: An ultrasonication-assisted green strategy. *Results in Chemistry,* 5 100944. https://doi.org/10.1016/j.rechem.2023.100944

[29] Yaseen A., Waseem M. A., Qadir M., Dar P. A., Hijazi S., Hussain M. A., and Shah W. A. (**2022**). PEG-400 catalyzed N-C, O-C & C-S bond formations: A robust sonication promoted synthesis of benzo[*d*]oxazole-2 (3*H*)-thione& benzo[*d*]thiazole-2(3*H*)-thione hybrids. *Analytical Chem. Lett.*, 12(3) 302-309. https://doi.org/10.1080/22297928.2022.2068376

[30] Hari Babu B., Vijay K., Krishna K. B. M., Sharmila N., and Baby Ramana M. (**2016**) An efficient PEG-400 mediated catalyst free green synthesis of 2-amino-thiazoles from α-diazoketones and thiourea. *J. Chem. Sci.,* 128(9) 1475-1478. https://doi.org/10.1007/s12039-016-1130-0

[31] Mekala R. S., Balam S. K., Harinath J. P. S., Gajjal R. R., Cirandur S. R., and Weaver G. (**2015**). Polyethylene glycol (PEG-400): An efficient medium for the synthesis of 1,2-disubstituted benzimidazoles. *Cogent Chemistry*, 1(1) 1049932. https://doi.org/10.1080/23312009.2015.1049932

[32] Nagaraju K., Gummidi L., Maddila S., and Jonnalagadda S. B. (**2020**) Polyethylene glycol (PEG-400) mediated one-pot green synthesis of 4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridines under catalyst-free conditions. *ChemistrySelect,* 5(40) 12407-12410. https://doi.org/10.1002/slct.202002538

[33] Patnala H., Abbo H. S., Potla K. M., Titinchi S. J. J., and Chinnam S. (**2019**) Polyethylene glycol (PEG-400): An efficient one-pot green synthesis and anti-viral activity of novel α-diaminophosphonates, *Phosphorus, Sulfur, and Silicon and the Relat. Elem.*, 194(11), 1035-1039, https://doi.org/10.1080/10426507.2019.1597365

[34] Hasaninejad A., and Beyrati M. (**2018**) Eco-friendly polyethylene glycol (PEG-400): a green reaction medium for one-pot, four-component synthesis of novel asymmetrical bis-spirooxindole derivatives at room temperature. *RSC Adv.,* 8(4) 1934-1939. https://doi.org/10.1039/c7ra13133j

[35] Lim H. Y., and Dolzhenko A. V. (**2023**) Polyethylene glycol as a green medium for the microwave-assisted synthesis of guanamines. *ChemistrySelect.* 8(29) e202302106. https://doi.org/10.1002/slct.202302106

[36] Ponduri R., Kumar P., and Vadali L. R. (**2018**) PEG-400 promoted a simple, efficient, and recyclable catalyst for the one-pot eco-friendly synthesis of functionalized isoxazole substituted pyrroles in aqueous medium. *Synth.Commun.*, 48(24), 3113-3122. https://doi.org/10.1080/00397911.2018.1535078

[37]Boddapati S. N. M., Tamminana R., Alam M. M., Gugulothu S., Varala R., and Bollikolla H. B. (**2021**) Efficient Pd(II)-catalyzed regioselective *ortho*-halogenation of arylcyanamides. *New J. Chem.,* 45 17176-17182. https://doi.org/10.1039/D1NJ01998H

[38] Rao G. V., Allaka T. R., Gandla M. K., Nanda P. K. V. V., Pindi S. R., Vaddi P. R. R., and Bollikolla H. B. (**2023**) Synthesis, antimicrobial activity, and *in silico* studies of fluoroquinolones bearing 1,3,4-oxadiazolyl-triazole derivatives. *J. Het.Com*., 60(10) 1666-1683. https://doi.org/10.1002/jhet.4700

[39]Merugu S. K., Krishnan V. B. R., Ansari S. A., Ansari I. A., and Bollikolla, H. B.(**2023**) Synthesis, anticancer evaluation and *in silico* studies of 1,4-dihydropyridines. *Chem. Biodivers.,* 20(8) e202201158. https://doi.org/10.1002/cbdv.202201158
[40] Atikala, V. K., Ansari S. A., Ansari I. A., Kumar R. K., and Bollikolla H. B. (**2024**) Synthesis of 2-aryl indazole: synthesis, biological evaluation and *in-silico* studies. C*hem. Biodivers.,* 20(8) e202201158. https://doi.org/10.1002/cbdv.202302085
[41] Bollikolla H. B., Anandam R., Chinnam S., Varala R., Khandapu B. M. K.,Kapavarapu R., Syed K. S., Dubasi N., and Syed M. A. (**2023**) *C*-Dimethylated flavones as possible potential anti-tubercular and anticancer agents. C*hem. Biodivers.,* 20(4) e202201201. https://doi.org/10.1002/cbdv.202201201
[42] Krishnan V. B. R., Merugu S. K., Gali S. J., Kapavarapu R., and Bollikolla H. B. (**2022**) Efficient multicomponent synthesis of Biginelli-dihydro-pyrimidines and evaluation of anti-cancer activity. *ChemistrySelect,* 7(29) e202201630. https://doi.org/10.1002/slct.202201630
[43] Chatterjee R., Mukherjee A., Zyryanov G. V., Majee A. (**2020**) Metal and solvent free direct C3-alkylation of 4-hydroxycoumarins with styrene. *AIP Conf. Proc.,* 2280 040011. https://doi.org/10.1063/5.0018529
[44] Alam M. M., Varala R., and Seema V. (**2024**) Zinc Acetate in organic synthesis and catalysis: A review. *Min. Rev. Org. Chem.*, 21 555-587. https://doi.org/10.2174/1570193X20666230507213511
[45] Babu H. B., Varala R., and Alam M. M. (**2022**) $Zn(OAc)_2.2H_2O$-Catalyzed Betti base synthesis under solvent free conditions. *Lett. Org. Chem.,* 19 14-18. https://doi.org/10.2174/1570178618666210616155257
[46] Reddy V. V. R., Saritha B., Ramu R., Varala R., and Jayashree A. (**2014**) $Zn(OAc)_2.2H_2O$-catalyzed one-pot efficient synthesis of aminonitriles. *Asian J. Chem.,* 26 7439-7442. https://doi.org/10.14233/ajchem.2014.17180
[47] Ramu E., Varala R., Sreelatha N., and Adapa S. R. (**2007**) $Zn(OAc)_2{\cdot}2H_2O$: A versatile catalyst for the one-pot synthesis of propargylamines. *Tetrahedron Lett.*, 48 7184-7190. https://doi.org/10.1016/j.tetlet.2007.07.196
[48] Kokane B. D., Varala R., and Patil S. G. (**2022**)$Zn(OAc)_2{\cdot}2H_2O$: An efficient catalyst for the one-pot synthesis of 2-substituted benzothiazoles. *Org. Commun*., 15 378-385.https://doi.org/10.25135/acg.oc.140.2210.2618
[49] Chinta B., Satyadev T. N. V. S. S., and Adilakshmi G. V. (**2023**) $Zn(OAc)_2{\bullet}2H_2O$-catalyzed one-pot synthesis of divergently substituted imidazoles. *Curr. Chem. Lett.*, 12 175-184.https://doi.org/10.5267/j.ccl.2022.8.007
[50] Pulle J. S., Totawar P. R., and Varala R. (**2023**) $Zn(OAc)_2{\cdot}2H_2O$-Catalyzed green synthesis of substituted 1-amido/thioamidoalkyl-2-naphthols. *Rev. Roum. Chim.*, 68 75-83.https://doi.org/10.33224/rrch.2023.68.1-2.07
[51] Mukherjee A., Mahato S., Zyryanov G. V., Majee A., and Santra S. (**2020**) Diverse synthesis of pyrano[3,2-*c*]coumarins: a brief update. *New J. Chem.*, 44 18980-18993. https://doi.org/10.1039/D0NJ03846F
[52] Hsieh W. C., Lin C. H., Yang Y. J., and Yang D. Y. (**2018**) Multicomponent synthesis of pyrano[2,3-*c*]coumarins. *RSC Adv*., 8(68) 39162-39169. https://doi.org/10.1039/c8ra06666c
[53] Douka M. D., and Litinas K. E. (**2022**) An overview on the synthesis of fused pyridocoumarins with biological Iinterest. *Molecules.* 27(21) 7256. https://doi.org/10.3390/molecules27217256
[54] Solovyev I.V., Zhukovsky D.D., Dar'in D.V., and Krasavin M.Y. (**2020**) *N*-Alkylation of nitrogen heterocycles with α-diazocarbonyl compounds. *Chem. Heterocycl. Comp.,* 56 809-813. https://doi.org/10.1007/s10593-020-02736-y
[55] Pavlinac I.B., Starčević K., Persoons L., Banjanac M., Radovanović V., Daelemans D., and Hranjec M. (**2024**) Novel iminocoumarinimidazo[4,5-*b*]pyridine derivatives: design, synthesis, and biological evaluation. *Chem. Heterocycl. Comp.,* 60 75-82. https://doi.org/10.1007/s10593-024-03296-1
[56] Sharapov A.D., Fatykhov R.F., and Khalymbadzha I.A. (**2024**) Synthesis of fluorophores based on benzo[*g*]coumarin framework (microreview). *Chem. Heterocycl. Comp.,* 60 26-28. https://doi.org/10.1007/s10593-024-03286-3
[57] Zavodskaya A.V., Parfenov V.E., Golovina O.V., and Bakharev V.V. (**2024**) A cascade reaction of 4-amino-substituted 6-hydrazinyl-1,3,5-triazin-2(1*H*)-ones with triethyl orthoacetate. *Chem. Heterocycl. Comp.,* 60 58-67. https://doi.org/10.1007/s10593-024-03294-3
[58] Vinokurov A.D., Iliyasov T.M., Karpenko K.A.,Akchurin, R.N., Derkach, Y.V., and Vereshchagin A.N. (**2023**) Highly diastereoselective synthesis of pyridinium-substituted piperidin-2-ones from pyridinium ylides, aldehydes, Michael acceptors, and ammonium acetate. *Chem. Heterocycl. Comp.,* 59 778-785. https://doi.org/10.1007/s10593-024-03271-w
[59] Lelyukh M., Paliy A., Zhukrovska M., Kalytovska M., Chaban I., Shelepeten L., and Chaban T. (**2024**) A review on synthetic approaches for obtaining and chemical modification of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole based heterocyclic compounds. *Curr. Chem. Lett.,* 13 737-752. 10.5267/j.ccl.2024.3.007
[60] Tolba M.S., Abd ul-Malik M.A., El-Dean A.M.K., Geies A.A., Radwan S.M., Zaki R.M., Sayed M., Mohamed S.K., and AbdelRaheem S.A.A. (**2022**) An overview on synthesis and reactions of coumarin based compounds. *Curr. Chem. Lett.,* 11 29-42. 10.5267/j.ccl.2021.9.007