WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 9, 909-918. Research Article ISSN 2277– 7105

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL N-ARYLATED CHROMONES

Srinivas A.[1], Hemasri Y.[2] and Jaya Prakash Rao Y.*[1,3]

[1]Department of Chemistry, University College of Science Rayalaseema university, Kurnool, Andhra Pradesh, India, 518002.

[2]Department of Chemistry, Nizam College, Basheer Bagh, Osmania University, Hyderabad, Telangana, India -500001.

[3]Department of Chemistry, University College of Science Osmania University, Hyderabad, Telangana, India -500007 and Department of Chemistry, University College of Science, Telangana University, Nizamabad, Telangana-503322.

Article Received on
06 March 2018,

Revised on 26 March 2018,
Accepted on 17 April 2018,

DOI: 10.20959/wjpr20189-12027

***Corresponding Author**
Jaya Prakash Rao Y.
Deportment of Chemistry, University college of Science Telangana university, Nizamabad, Telangana-503322.

ABSTRACT

A series of new N-arylated chromones were synthesized from 2-amino chromones and variety of aryl halides employing Pd-catalyzed Buchwald–Hartwig coupling The products may be used as precursors for synthesis of potentially relevant targets. The structures of all synthesized compounds were established based on IR, ^{1}H NMR and ^{13}C NMR and MS spectral analysis. The synthesized compounds were screened for their anti bacterial activity against gram positive bacteria *B.subtilis* and *S.aureus*, gram negative bacteria *E.coli* and *P.aeruginosa*, and anti fungal activity aganist *A.niger* and *A.flavus*. The compound 7g showed excellent activity against *B subtitle* and 7g, 7h exhibited promising anti fungal activity against *A.niger*.

KEYWORDS: 2-Amino chromone, aryl halides, Buchwald–Hartwig coupling and N-aryl 2-amino chromones.

1. INTRODUCTION

Chromones are widely occurs, in several bio active natural and synthetic targets. These compounds shows significant pharmacological activities, such as anti-inflammatory,[1] antitumoral,[2] P-glycoprotein binding (to overcome multidrug resistance),[3] neuroprotective,[4] HIVinhibitory,[5] antitumorals, antioxidant,[6] antifungal and

antimicrobial,[7] Inhibition of enzymes like oxidoreductases, kinases,[8,9] antiasthmatics,[10] and cyclooxygenases.[11] 2-amino chromones are a close or heterocyclic's possess anti platelet activity.[12]

The Buchwald–Hartwig C-N coupling is a lightly efficient and widely used tool to prepare subsisted aryl amines. The reaction has gained much prominence primary and secondary amines because it is suitable for large-scale synthesis industrial and fine chemicals and in organic synthesis.[13-15] The main advantages of Buchwald–Hartwig reaction are mild reaction conditions and easy availability of a wide range of hetrocyclic and aryl and hetro cyclic halides[16] Buchwald–coupling it proceeds well in the presence of base, $Pd_2(dba)_3$ and xanthopous, The non toxic by product (inorganic) easily removed from the reaction mixture. In view of biological activity of chromone derivatives and C-N bond formation, we planned for the synthesis of new N-arylated chromone derivatives by adopting N-arylated, Pd-catalyzed Buchwald–Hartwig coupling. To the best of our knowledge, there are no reports in the literature on N-C bond formation at 2-amino chromones.

2. MATERIALS AND METHODS

The uncorrected melting points of compounds were determined using open capillary in a paraffin bath. All the reagents utilized were commercial and laboratory grade. IR spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^{1}H NMR spectra were obtained on Varian 400 MHz instrument, with TMS as internal reference and chemical shifts are expressed in δ ppm solvent used in $CDCl_3$ (for intermediate compounds) and DMSO-D_6 (for final compounds) and mass spectrum on a Hewelett Packard mass spectrometer operating at 70 ev, purity of the compounds tested by TLC, which is performed with E. Merck pre coated silica gel plates (60 F-254) with iodine as a developing agent. Acme, India silica gel, 60-120 mesh used for column chromatography.

2.1 EXPERIMENTAL SECTION

2.1.1 Preparation of (E)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (2a)

To a stirred solution of 2-hydroxy acetophenone (**1a**) (1 mmol) in DMF-DMA (10 mmol) was stirred at 80–90 °C. A clear solution was observed after 30 min, a yellow precipitate began to appear. After stirring for 2 hour under these conditions, the reaction mixture was filtered, washed with light petroleum ether and dried. The solid was recrystallised from $CHCl_3$ to afford title compound (**2a)** as bright yellow solid; yield: 75%; ^{1}H-NMR (400MHz,

$CDCl_3$): δ 9.3 (d, 1H, *J* = 6.0 Hz), 7.50-7.95 (m, 3H), 7.15 (d, 1H, *J* = 4.0 Hz), 6.12 (d, 1H, *J* = 6.0 Hz), 5.15 (brs, 1 H), 3.1 (s, 6 H); MS (ESI): m/z 192 $(M+H)^+$.

2.1.2 Preparation of 2-(isoxazol-5-yl)phenol (3a)

To a stirred solution of (E)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (**2a) (**1 mmol**)** in EtOH (15 mL) solution added $NH_2OH{\cdot}HCl$ (1.5 mmol). The reaction mixture was refluxed for 1 hour on water bath. Within 5 min, the yellow colour of the enamino ketone was **5** disappeared. Further the reaction mixture was heated for 30 min. Solvent was removed under reduced pressure. Ice-cold water(10 mL) was added to the residue, white precipitate was obtained and filtered off, washed with water, dried in air and recrystallised (EtOAc–light petroleum) to afford white crystalline solid 2-(isoxazol-5-yl)phenol **(3a):** yield: 65%; off-White solid; IR: 3250, 1625, 1575, 1135 $cm^{-}1$. ^{1}H-NMR (400MHz, $CDCl_3$) : δ 10.38 (s, exchangeable, 1H), 8.45 (d, 1H, *J* = 1.5 Hz), 7.70 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.15–7.30 (m, 3H), 6.95 (d, 1H, *J* = 1.5 Hz); MS (ESI)**:** m/z 162 $(M+H)^+$.

2.1.3 Preparation of 2-amino-4H-chromen-4-one (5a)

To a stirred solution of 2-(isoxazol-5-yl)phenol (1mmol) **(3a)** in DMF (10 mL) added triethylamine (2 mmol). The reaction mixture was heated in an oil bath, maintaining the temperature at 140–150°C for 8 hour. The solvent DMF was removed under reduced pressure and ice-cold water was added to the residue. The separated solid was filtered off and recrystallised from MeOH to get pale yellow crystalline compound 2-amino-4H-chromen-4-one **(5a):** yield: 55%; pale yellow crystalline solid; IR: 3303, 3098, 1644, 1609, 1546, 1276, 755 $cm^{-}1$. ^{1}H-NMR (400MHz, $CDCl_3$,): δ 7.90 (dd, 1H, *J* = 7.7, 1.4 Hz). 7.57–7.63 (m, 1H), 7.53(s, exchangeable, 2H), 7.32–7.38 (m, 2H), 5.19 (s, 1H); MS (ESI): m/z 162 $(M+H)^+$.

2.1.4 General method for the preparation of N-arylated 2-amino chromones (7a-h)

2-Amino-4H-chromen-4-one (**5a-b)** (1.2 mmol) was mixed with halo compounds (**6a-d)** (1.2 mmol) in 1,4-dioxane solvent. The reaction mixture was degassed by bubbling the nitrogen through the solution for 30 min. Later, Xanthopous (0.025 mmol), $Pd_2(dba)_3$ (0.025 mmol) and NaOt-Bu (1.5 mmol) was added to the same flask at room temperature and the mixture was stirred for 10 min under nitrogen atmosphere. Then the reaction mixture was heated to 90^{o}C for 6 hours. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine solution and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to give crude product which was

purified by column chromatography using silica gel (60-120 mesh) by eluting with 2% methanol-DCM as solvent, gave the title compounds **7a-h**.

2-(3-propionylpyridin-2-ylamino)-4H-chromen-4-one (7a): Yield: 66%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 7.95 (d,1H, *J* = 12.0 Hz), 7.4 (dd, 2H), 7.65 (t,1H, *J* = 16.0 Hz), 7.05 (s, NH), 6.95 (s, 2H), 7.0 (s, 1H), 6.90 (s, 1 H), 2.28 (s, 6 H); ^{13}C-NMR (125MHz, DMSO-D_6): δ 173.5, 162, 152.5, 137, 133.2, 132.8, 129, 128.3, 125.4, 124, 123.2, 117, 99.2, 20.4. mp 180-183^{o}C; MS (ESI) m/z $(M+H)^{+}$: 266.

2-(6-methoxypyridin-2-ylamino)-4H-chromen-4-one (7b): Yiled: 68%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 8.10 (d,1H, *J* = 12.0 Hz), 7.65-7.80 (m,3H,), 7.45 (t,1H, *J* = 16.0 Hz), 7.25 (d, 2H, *J* = 12.0 Hz), 7.10 (s, 1H), 7.0 (s, NH), 6.95 (d, 2H, *J* = 18.0 Hz), 6.75 (s, 1 H), 4.75 (s, 3 H); ^{13}C-NMR (125MHz, DMSO-D_6): δ175.5, 161, 151.5, 146.5, 132.2, 129.8, 128, 126.3, 124.4, 123.7, 118.8, 113, 109.2, 106.2, 96.2, 54.4. mp 188-192 ^{o}C; MS (ESI) m/z $(M+H)^{+}$: 269.

2-(3,5-dimethylphenylamino)-4H-chromen-4-one (7c): Yiled: 65%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 8.25 (d,1H, *J* = 16.0 Hz), 7.90-8.0 (m,2H,), 7.70-7.78 (m, 3H), 7.60 (t,1H, *J* = 12.0 Hz), 7.25 (s, NH), 6.80 (s, 1H), 3.45 (m, 2 H), 1.20 (t,3H, *J* = 14.0 Hz); mp 182-185^{o}C; ^{13}C-NMR (125MHz, DMSO-D_6): δ 195.2, 178.3, 170.8, 152, 150.3, 147, 134.4, 132, 125.6, 123, 122.5, 118, 116.3, 113, 92.6, 38.2, 8.5. MS (ESI) m/z $(M+H)^{+}$:295.

2-(benzo[d][1,3]dioxol-7-ylamino)-4H-chromen-4-one (7d): Yiled: 70%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 8.0 (d,1H, *J* = 14.0 Hz), 7.55-7.70 (m, 3H), 7.15 (t,1H, *J* = 16.0 Hz), 7.05 (s, NH), 6.90 (m, 2H), 6.80 (s, 2H), 6.75 (s,1H); mp 235-238^{o}C; ^{13}C-NMR (500MHz, DMSO-D_6): δ 178.2, 167, 154.8, 150.9, 140, 138.3, 133.8, 131.3, 128.4, 127.6, 127, 122, 116.8, 115.7, 106, 90.8. MS (ESI) m/z $(M+H)^{+}$: 282.

2-(3-propionylpyridin-2-ylamino)-6-chloro-7-methoxy-4H-chromen-4-one(7e): Yiled: 71%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 7.7 (s,1H), 7.45-7.55 (m,2H), 7.15 (s, 2H), 6.90 (s, NH), 6.85 (s, 1H), 3.95 (s, 3 H), 2.30 (s, 6 H); ^{13}C-NMR (125MHz, DMSO-D_6): δ 175.5, 163, 154.5, 139.2, 134.2, 133.2, 129.9, 128.2, 126.2, 125, 124.2, 119, 99.8, 38.4, 21.8. mp 238-242^{o}C; MS (ESI) m/z $(M+H)^{+}$:330.

2-(6-methoxypyridin-2-ylamino)-6-chloro-7-methoxy-4H-chromen-4-one (7f): Yiled: 67%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 7.85 (s,1H), 7.45 (t,1H, *J* = 16.0 Hz), 7.20 (s,1H),

7.15 (d,1H, *J* = 14.0 Hz), 7.10 (s, 1H), 7.05 (s, NH), 6.95 (d,1H, *J* = 14.0 Hz), 6.83 (s, 1 H), 3.85 (s, 6 H); ^{13}C-NMR (125MHz, DMSO-D_6): δ173.5, 158.8, 149.5, 146.8, 130, 128.5, 128, 126.3, 125.4, 124.7, 116.2, 110.8, 109.2, 107.2, 97.8, 50.4, 47.8. mp 275-278^{o}C; MS (ESI) m/z $(M+H)^+$:333.

2-(3,5-dimethylphenylamino)-6-chloro-7-methoxy-4H-chromen-4-one (7g): Yiled: 69%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 8.35 (d,1H, *J* = 14.0 Hz), 8.00 (d,1H, *J* = 14.0 Hz), 7.90 (s,1H), 7.70 (t,1H, *J* = 16.0 Hz), 7.60 (s, 1H), 6.95 (s, NH), 6.80 (s, 1H), 3.90 (s, 3H), 3.45 (m, 2 H), 1.20 (t,3H, *J* = 14.0 Hz); ^{13}C-NMR (125MHz, DMSO-D_6): δ 198.2, 178.2, 171.8, 154, 150.5, 147.8, 135.6, 134, 127.8, 126, 123.5, 116, 115.3, 112.6, 94.6, 42.2, 38.2, 8.2. mp 233-235^{o}C; MS (ESI) m/z $(M+H)^+$: 359.

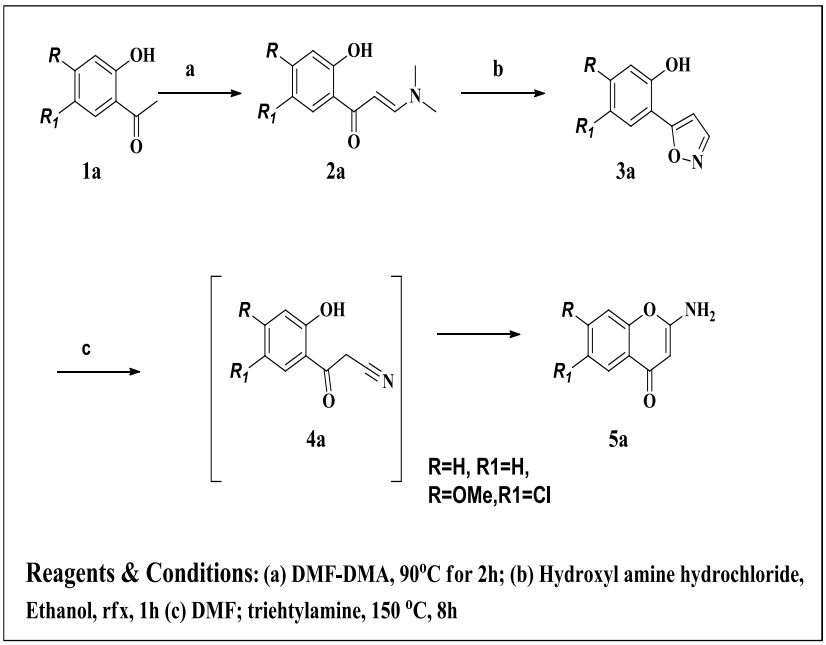
2-(benzo[d][1,3]dioxol-4-ylamino)-6-chloro-7-methoxy-4H-chromen-4-one(7h): Yiled: 61%; ^{1}H-NMR (400MHz, DMSO-D_6): δ 7.90 (s,1H), 7.35-7.40 (m,2H), 7.15 (m, 2H), 7.05 (s, NH), 6.95 (s,2H), 6.80 (s, 1 H), 3.90 (s, 3 H); ^{13}C-NMR (125MHz, DMSO-D_6): δ 178.8, 167.6, 155.2, 151.9, 142, 138.8, 134.8, 132.3, 130.4, 128.6, 126.2, 120.4, 117.2, 116.7, 105, 93.8, 55.8. mp 262-265^{o}C; MS (ESI) m/z $(M+H)^+$:346.

3.0 RESULTS AND DISCUSSION

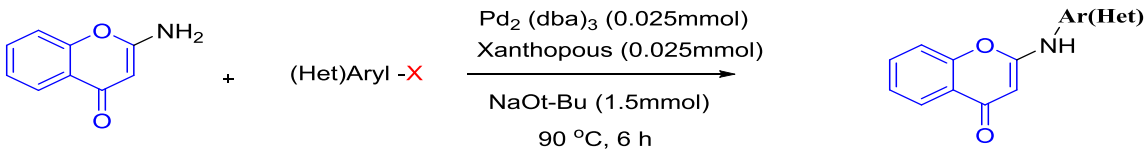
3.1 CHEMISTRY

Compound **3a** was prepared from 2-Hydroxy acetophenone **1a** according to a procedure in the literature (scheme 1). 2-Hydroxy acetophenone **1a** was reacted with DMF-DMA to obtain (E)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one **2a** which was heated with $NH_2OH.HCl$ in EtOH under reflex condition for 30 min to give desired 2-(isoxazol-5-yl)phenol **3a.** The intermediate **3a** with triethylamine in DMF at 150^{O}C for 8 hours afforded desired key precursor of final products 2-amino chromone **5a.**[17]

The coupling of the substrate **5a** with aryl halide **(6a-d)** in the presence of $Pd_2(dba)_3$, xanthopous and NaOt-Bu in 1,4-Dioxane at 90^{o}C afforded the corresponding N-arylated 2-amino chromones **7a-h** in moderate to good yields(scheme 2). The structures of compounds **7a-h** were confirmed by spectral analysis.

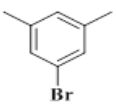
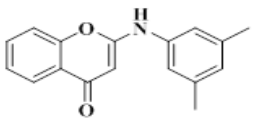
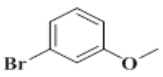
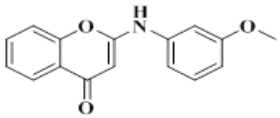
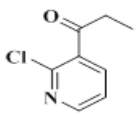
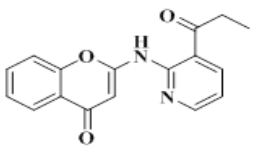
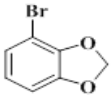
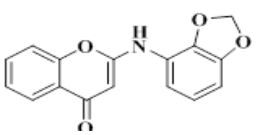


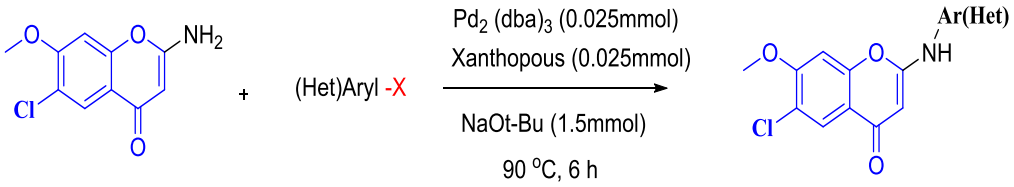
Scheme 1: synthesis of 2-amino-4H-chromen-4-one 5a.



Scheme 2A: synthesis of N-arylated 2-amino chromones 7a-d.

Table 1.

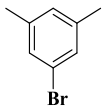
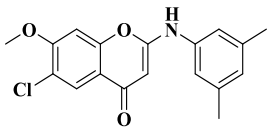
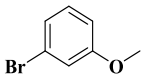
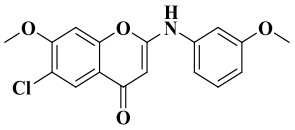
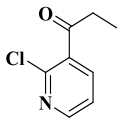
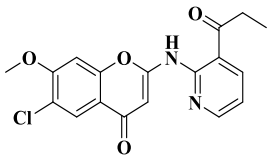
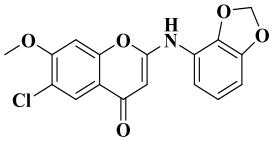
Entry	Substrate	Product
7a		
7b		
7c		
7d		



5b **6a-d** **7e-h**

Scheme 2 B: synthesis of N-arylated 2-amino chromones 7e-h.

Table 2.

Entry	Substrate	Product
7e		
7f		
7g		
7h		

3.2 Antibacterial activity

The newly synthesized final compounds **(7 a-h)** were screened for their antibacterial activity against a gram-positive bacteria *S. aureus*, *B. subtilis* and gram-negative bacteria *E. coli*, *P. aeruginosa*. the compound **7 g** was found to exhibit excellent activity as compared to the standard drug ampicillin againest gram positive bacteria *B subtilis* Other compounds were found to possess poor activity. On testing the activity against *S. aureus*, compound **7h** shows good activity. On evolution of the compounds against *E. coli* **7 g** and **7 h** were found to exhibit good activity. However compounds **7 c** and **7d** were found to possess moderate activity as compared to the standard drug. Compound **7 h** showed excellent activity against

P.auruginosa as compared to the standard drug streptomycin, compounds **7a, 7 b, 7c** and 7 d were found to have moderate activity against the same bacterial strain.

3.3 Antifungal activity

The antifungal tests were carried out against two different fungal strains A. niger and A. flavus, where nystatin was used as a standard drug. Antifungal property of the synthesized derivatives was found to be more effective on *A. niger* as compared to A. flavus. against A. niger, The compounds **7 g** and **7 h** were found to exhibit higher activity against as compared to the standard drug nystatin. However compounds **7 a, 7 b, 7 c** and **7d** were found to possess significant activity. Compounds **7 f, 7 g** and **7h** were exhibited moderate activity against *A. flavus*. However compound **7 a** possessed good activity against the same fungal strain.

Table 3: Antibacterial and antifungal activity data of compounds (7a-h).

Compounds	Minimum Inhibitory Concentration (MIC) in µg/ml					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	B. subtilis	*S. aureus*	*E. coli*	*P.aeruginosa*	*A. niger*	*A. flavus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
7a	1000	1000	1000	150	250	125
7b	900	1000	1000	150	250	1000
7c	1000	1000	250	150	250	1000
7d	1000	1000	250	150	1000	1000
7e	1000	1000	1000	1000	1000	1000
7f	1000	1000	250	250	**94.5**	250
7g	**64.5**	800	125	1000	**84.5**	250
7h	1000	250	125	**49.5**	500	250

4.0 CONCLUSIONS

A simple and efficient method for the synthesis of new N-arylated 2-amino chromones **7a-h** using the Buchwald–Hartwig C-N cross coupling reactions was described. These compounds may be useful for the development of new bio-active compounds.

5.0 ACKNOWLEDGEMENT

This work was supported by Dept. of Chemistry, University College of Science, Rayalaseema University, Kurnool, Andhra Pradesh, India- 518002, Dept. of Chemistry, University College of Science, TelanganaUniversity, Nizambad, Telangana-503322 and Dept. of Chemistry, University College of Science, Osmania University, Hyderabad, Telangana, India -500007.

6.0 CONFLICT OF INTEREST

"The author(s) declare(s) that there is no conflict of interest regarding publication of this article".

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