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Facile synthesis of highly functionalized aromatic novel 3-(2,4-substituted diaryl-2*H*-chromen-3-yl)-5-phenylisoxazole derivatives

Madhu Gutam[a], Santosh Kumar Konda[b], Naveen Reddy Vadiyala[a], Gangadhar Thalari[a], Jayaprakash Rao Yerrabelli[a] & Prasad Rao Chitneni*[a]

[a] Natural Products Laboratory, Department of Chemistry, Osmania University, Hyderabad 500 007, Telangana, India
[b] Department of Chemistry, Geethanjali College of Engineering and Technology (Autonomous), Cheeryal, Hyderabad 501 301, India
E-mail: prasadraoou@yahoo.com

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An efficient approach has been described for the synthesis of substituted diaryl aromatic flava none-isoxazole (**7a-m**) hybrids through simple and practical methodology. The synthetic strategy involves formation of substituted diaryl flavanone aldoxime intermediates (**5a-k**) from substituted flavanone -3- aldehydes (**4a-k**). This is followed by [3+2] cycloaddition of *in situ* generated nitrile oxides with aryl acetylenes using sodium hypochlorite oxidant in THF in absence of light, to furnish the functionalized isoxazoles with excellent yields (85-90%).

Keywords: Flavanone, Suzuki cross-coupling, 1,3-Dipolar cycloaddition, Isoxazole

Flavanone and its derivatives are vital scaffolds and useful synthetic building blocks in heterocyclic and medicinal chemistry[1]. Flavanones are having obviously diverse biological activities with specific targets for example naringenin used as human breast cancer cell proliferation inhibitor[2], hesperetin as cell cycle arrest[3] and hesperidin for reduction of *in vivo* metastatic potential[4]. Isoxazole motifs were most significant five membered heterocyclics having oxygen and nitrogen implanted in several biologically active natural products and drugs[5]. Isoxazole is the key constituent of regularly used synthetic product[6]. Several lifesaving drugs, pharmaceuticals and bioactive natural products integrate with isoxazole as an important pharmacophore pivotal to their potential biological activities. Isoxazole based natural products and potential drugs shown in Fig. 1. Wherein oxacillin used as a β-lactam antibiotic[7], valedcoxib as COX-2 inhibitor[8], sulfamethoxazole as PABA antagonist[9], leflunomide as anti-rheumatic drug[10], ibotenic acid as neurotoxin[11], zonisamide as an anti-convulsant[12] and anti-obesity agent[13].

Based on the literature, isoxazole having contiguous electronegative heteroatoms those are capable of fascinating in hydrogen donor-acceptor interactions therefore isoxazole used as requisite synthon for enforcing the anticipated pharmacological activities[14]. Owing to their impressive medicinal properties of isoxazole, organic and medicinal chemists focused on synthesis of isoxazole based synthetic libraries and semi synthetic natural product derivatives[15]. Recently various approaches have been reported for the synthesis of isoxazole executed with 1,3-dipolar cycloaddition[16,17]. Inspired by these observations we described our effort in a systematic synthesis of isoxazole derivatives on flavanone skeleton.

Results and Discussion

In this context, we explored the synthetic versatility of highly aryl substituted flavanone and isoxazole hybrids in present work. The target compounds were obtained in following steps. Initially, flavanone derivatives (**1a-e**) were synthesized by our previously reported procedure[18], subsequently Vilsmeier-Haack reaction was carried out in presence of DMF/ $POCl_3$ to yield 4-chloro-2-aryl-2*H*-chromene-3-carbaldehydes (**2a-e**) respectively[19]. Compounds (**2a-e**) were subjected to regioselectively Suzuki cross-coupling with aryl boronicacids (**3a-c**) at C-4 position to obtain 2,4-diaryl-2*H*-chromene-3-carbaldehydes (**4a-k**) [20]. The key intermediates 2,4-diaryl-2*H*-chromene-3-carbaldehyde oximes (**5a-k**) were synthesized by hydroxylamine hydrochloride condensation with compounds (**4a-k**) in the presence of sodium acetate in THF:MeOH:H_2O (1:1:1) under reflux conditions. Finally, aryl alkynes (**6a-c**) were underwent 1,3-dipolar cycloaddition with *in situ*

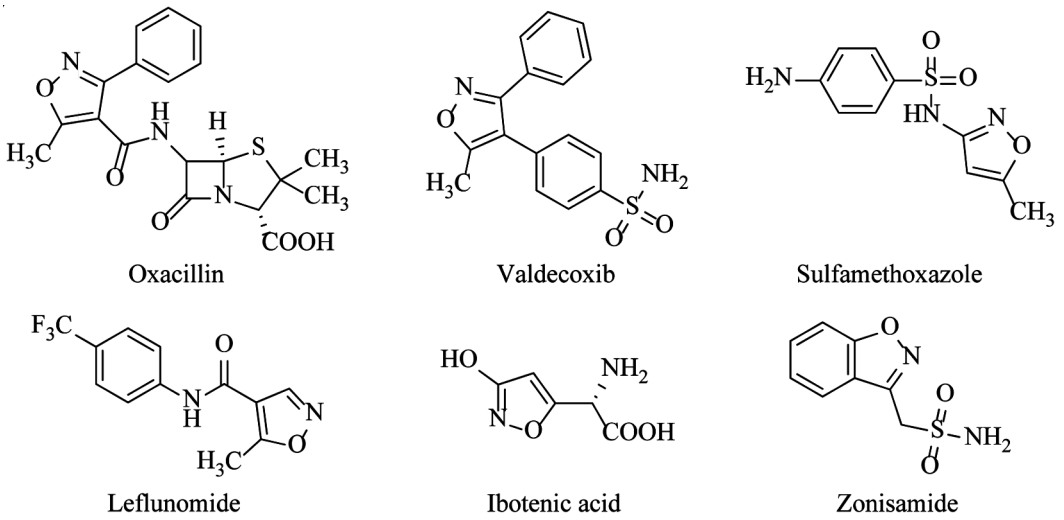


Fig. 1 — Isoxazole based biologically active natural products and drugs

generated nitrile oxides from compounds (**5a-k**) in the presence of sodium hypochloride in THF in absence of light (dark) to give 3-(2,4-diaryl-2*H*-chromen-3-yl)-5-arylisoxazoles (**7a-m**) in good yields (Scheme 1). All the synthesised compounds structures were established by ^{1}H and ^{13}C NMR and ESI-MS.

Experimental Section

All chemicals were purchased from Sigma-Aldrich and solvents from SD Fine Chemicals Pvt. Ltd. Solvents were purified as per the procedures given in the "Text book of practical organic chemistry" by Vogel (6th Edition). Silica gel pre-coated aluminum sheets (60F254, Merck) were used for monitoring the progress of reaction and purity of final products. The spots on TLC plates were visualized by exposure to ultraviolet light (UV) at 254 nm. Column chromatography was performed using Merck silica gel 60-120 mesh. ^{1}H NMR spectra were recorded on Bruker spectrometer at 400 MHz spectrometer, ^{13}C NMR spectra were acquired on 100MHz with tetramethylsilane as an internal standard, chemical shifts are reported in δ (ppm). Chemical shift is denoted by δ (multiplicity, coupling constant, proton count). Mass spectral analysis was accomplished using electro spray ionization (ESI) techniques.

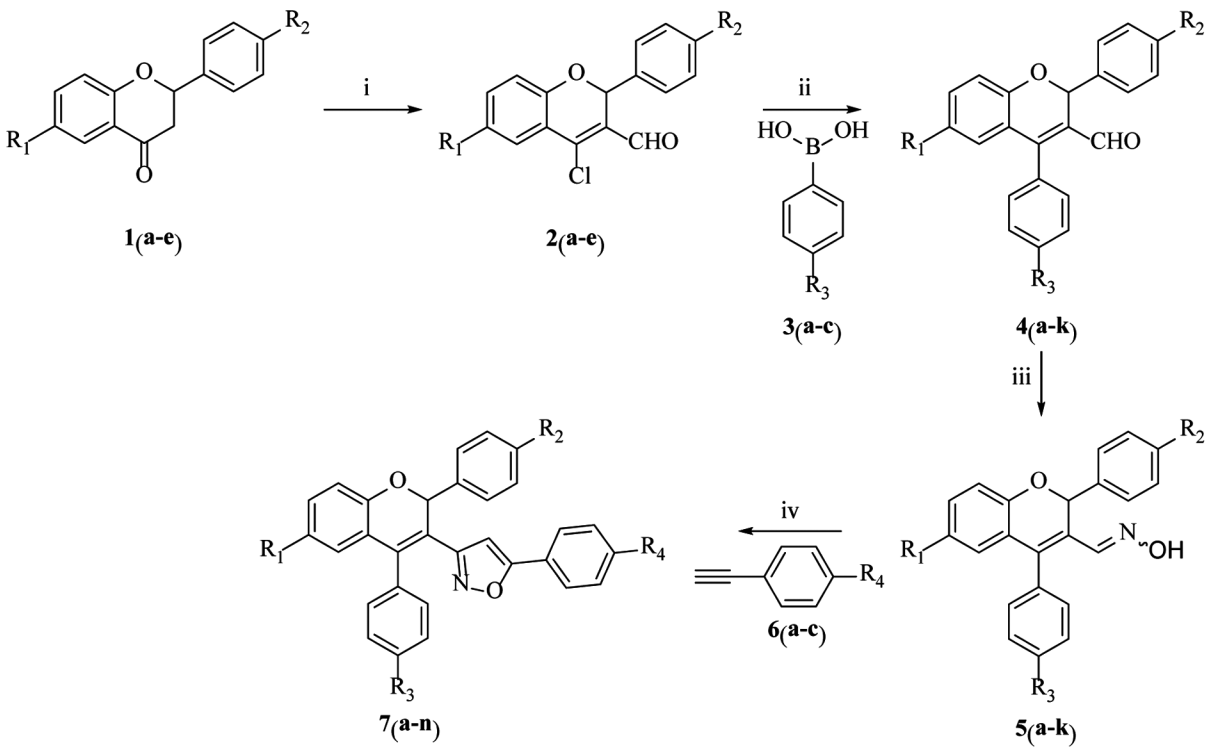
General procedure for the synthesis of 2,4-diaryl-2*H*-chromene-3-carbaldehydes, 4a-k

4,6-Dichloro-2-phenyl-2*H*-chromene-3-carbaldehyde **2a** (0.346g, 1 mmol) was stirred in the presence of 10 mol% tetrakis (triphenylphosphene) palladium (0) at RT in dry DMF (15 mL) and Na_2CO_3 (0.318g, 3 mmol) and the solution was degassed by bubbling the nitrogen through the solution for 30min. Phenylboronic acid **3a** (0.366g, 3 mmol) in dry DMF was added and the mixture was stirred for 30mins under nitrogen atmosphere. The reaction mixture was heated at 80°C for 4 h, cooled and poured into crushed ice. Then the reaction mixture was extracted with ethylacetate (3×10 mL), washed with water (3×3 mL). The aqueous layers were combined and further extracted with ethylacetate (3×5 mL). The combined organic layers were dried with anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography using pet.ether: ethylacetate (8:2) to give 6-chloro-2,4-diphenyl-2*H*-chromene-3-carbaldehyde **4a**.

6-Chloro-2,4-diphenyl-2*H*-chromene-3-carbaldehyde, 4a: Yield 80%. Yellow solid. m.p.125-128°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.53 (m, 4H), 7.40 (m, 2H), 7.32 (m, 4H), 7.22 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H) 6.43 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 190.4, 153.1, 150.0, 138.6, 132.9, 132.1, 130.7, 129.7, 129.4, 128.9, 128.6, 128.5, 127.8, 126.9, 126.5, 124.2, 119.0, 73.5; ESI-MS: *m/z* 347 [M+H], 369 $[M+Na]^{+}$, 371$[M+Na+2]^{+}$. Anal. Calcd for $C_{22}H_{15}ClO_2$: C, 76.19; H, 4.36. Found: C, 76.21; H, 4.34%.

General procedure for the synthesis of 2,4-diaryl-2*H*-chromene-3-carbaldehyde oximes, 5a-k

6-Chloro-2,4-diphenyl-2*H*-chromene-3-carbaldehyde **4a** (0.200g, 0.57 mmol) was stirred in the presence of



7a; R_1=Cl, R_2=H, R_3=H, R_4=H
7b; R_1=Cl, R_2=CH_3, R_3=H, R_4=H
7c; R_1=Cl, R_2=H, R_3=F, R_4=H
7d; R_1=Cl, R_2=CH_3, R_3=F, R_4=H
7e; R_1=Cl, R_2=H, R_3=OCF_3, R_4=H
7f; R_1=Cl, R_2=CH_3, R_3=OCF_3, R_4=H
7g; R_1=Cl, R_2=H, R_3=H, R_4=OCH_3
7h; R_1=H, R_2=H, R_3=H, R_4=H
7i; R_1=H, R_2=CH_3, R_3=H, R_4=H
7j; R_1=H, R_2=OCH_3, R_3=H, R_4=H
7k; R_1=H, R_2=H, R_3=H, R_4=CH_3
7l; R_1=H, R_2=H, R_3=H, R_4=OCH_3
7m; R_1=H, R_2=OCH_3, R_3=H, R_4=CH_3

Reagents and Conditions: (i) DMF, $POCl_3$, 0°C-RT, 2 h, 80%; (ii) $Pd(PPh_3)_4$, Na_2CO_3, DMF, 100°C, 4 h, 70-80%, (iii) NH_2OH, CH_3COONa, CH_3OH:H_2O:THF (1:1:1), reflux, 3 h, 70-80%; (iv) NaOCl, THF, RT, 3 h, 85-90%.

Scheme 1 — Synthetic scheme for the synthesis of 3-(2,4-diaryl-2*H*-chromen-3-yl)-5-arylisoxazoles (**7a-m**)

hydroxylamine hydrochloride (0.08g, 1.1 mmol), sodium acetate (0.09g, 1.1 mmol), tetrahydrofuran as a solvent, methanol and water (1:1:1) ratio under reflux condition for 3 h. The progress of the reaction was monitored by TLC, the reaction mixture was poured into ice cold water and extracted with ethylacetate (3×10 mL), washed with water (3 mL). The combined organic layers were dried with anhydrous sodium sulphate and concentrated under reduced pressure. The separated solid was conformed as 6-chloro-2,4-diphenyl-2*H*-chromene-3-carbaldehyde oxime **5a**.

6-Chloro-2,4-diphenyl-2*H*-chromene-3-carbalde hyde oxime, 5a: Yield 80%. White solid. m.p.155-159°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, -CH=N-, 1H), 7.49-7.43 (m, 6H), 7.32-7.27 (m, 5H), 7.07-7.04 (m, 1H), 6.79-6.77 (m, 1H), 6.70-6.69 (m, 1H), 6.39 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 151.0, 148.0, 138.5, 137.9, 129.8, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.0, 126.1, 125.8, 125.0, 124.5, 118.1, 74.2; ESI-MS: *m/z* 362 $[M+H]^+$, 364 $[M+H+2]^+$. Anal. Calcd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46. Found: C, 73.06; H, 4.48%.

General procedure for the synthesis of 3-(2,4-substitued diaryl-2*H*-chromen-3yl)-5 aryl isoxa zoles, 7a-m

6-Chloro-2,4-diphenyl-2*H*-chromene-3-carbaldehyde oxime **5a** (0.1g, 0.28 mmol) was stirred in the presence of sodium hypochlorite (0.06g, 8 mmol), phenyl acetylene **6a** (0.03g, 0.3 mmol) in tetrahydrofuran as a solvent under RT for 12 h. The progress of the reaction was monitored by TLC, the reaction mixture was extracted by ethylacetate (3×10 mL) and washed with water (3 mL). The combined organic layers were dried with anhydrous sodium sulphate, concentrated vacuo and purified by column chromatography using pet.ether: ethylacetate (9:1) to afford compound **7a**.

3-(6-Chloro-2,4-diphenyl-2*H*-chromen-3yl)-5-phenylisoxazole, 7a: Yield 90%. Light yellow solid. m.p.190-194°C. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.61-7.58 (m, Ar-H, 5H), 7.48-7.45 (m, Ar-H, 3H), 7.39-7.37 (m, Ar-H, 4H), 7.35-7.31 (m, Ar-H, 3H), 7.13-7.11 (m, Ar-H, 1H), 6.87-6.85 (m, Ar-H, 1H), 6.79 (m, Ar-H, 1H), 6.73 (s, 1H), 5.24 (s, 1H); ^{13}C NMR (100.6MHz, $CDCl_3$): δ 168.7, 160.4, 151.1, 138.4, 137.2, 135.9, 130.2, 130.0, 129.4, 128.9, 128.8, 128.6, 128.5, 127.7, 127.1, 126.5, 126.2, 125.6, 125.5, 121.5, 118.4, 99.2, 76.3; ESI-MS: *m/z* 462 $[M+H]^+$, 464 $[M+H+2]^+$. Anal. Calcd for $C_{30}H_{20}ClNO_2$: C, 78.00; H, 4.36. Found: C, 78.03; H, 4.34%.

Conclusion

In summary, we report a simple and efficient synthetic methodology for the synthesis of highly aryl/heteryl substituted flavanone based isoxazole hybrids by adopting multistep synthetic strategy involving C-4 regioselective Suzuki cross-coupling and 1,3-dipolar cycloaddition in absence of light with excellent yields. This methodology will be very useful for the synthesis of substituted diaryl flavanone derivatives and also valuable tool for future endeavor.

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