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A SIMPLE SYNTHESIS OF 2- AMINO-4-THIOPHENYL-4H,5H-[1]-BENZO PYRANO[4,3-B]-PYRAN-3-CARBONITRILES AND EVALUATION OF ANTIBACTERIAL ACTIVITY

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Abstract
Synthesis of novel densely functionalized 2-amino-4-thiophenyl-4H,5H-[1]-benzo pyrano[4,3-b]-pyran-3-carbonitriles **3a-e** has been accomplished by the Michael addition of malononitrile to the *α,β*-unsaturated -3-thiophenylidene-4-chromonones **2a-e.** The antibacterial activity of new compounds evaluated.

Key words: chromonones, Michael addition, 3-thiophenylidene-4-chromonones

Introduction

4-chromonones are versatile intermediates for the synthesis of many natural products such as brazilin, hematoxylin, ripariochromene, clausenin, calanolide(A) and nophyllum(B)[1,2]. Eucomine, the first member of arylidene chromonone has been isolated from *Eucomis bicolor*(3). Chromonone heterocycles have also drawn much attention because of their important pharmacological properties[1], high activity against anti-human immunodeficiency virus type-1(HIV-1) [4]. The derivatives of 4-chromonone have activity against trichomands and fungi[5,6]. 4H,5H-[1]- benzo thio pyrano[4,3- b]- pyran -4-one and 1,4 dihydro-5H-[1] benzothiopyrano[4,3-b]pyridine-4-one derivatives have anti allergic and antifungal activity[7,8]. In view of pharmacological activity of the chromonone derivatives and arylidene chromon-4-ones, we have synthesized novel 2- amino-4-thiophenyl-4H,5H-[1]-benzopyrano[4,3-b]-pyran-3-carbonitriles by the cyclization of 3- thiophenylidene -4-chromonones with malononitrile and all the newly synthesized compounds screened for antibacterial activity.

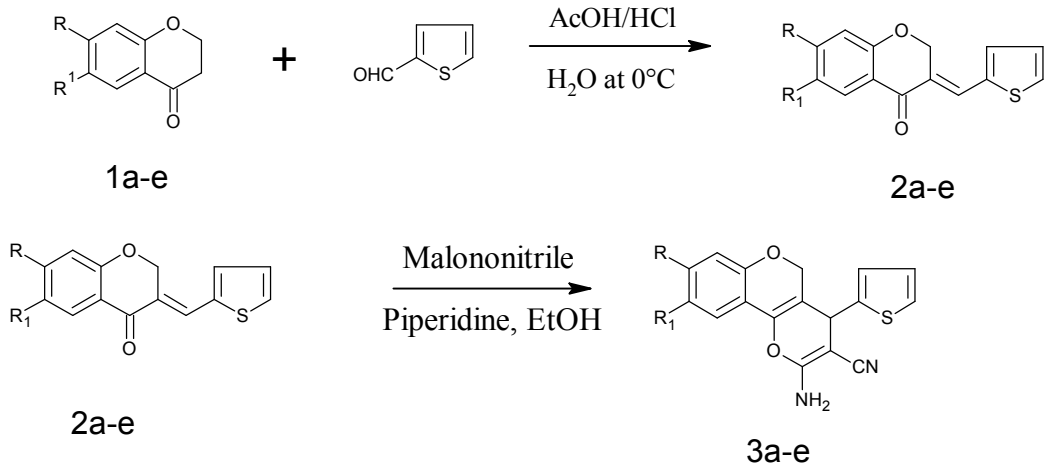
Results and Discussion

The *α,β*-unsaturated -3-thiophenylidene-4-chromonones **2a-e** containing exocyclic double bonds as dipolarophiles were prepared by the acid catalyzed reactions of various 4-chromonones **1a-e** with thiophene-2-aldehyde and the products were assigned E-configuration based on the ^{1}H-nmr data[9]. In its IR(KBr) spectrum **2a** showed the carbonyl peak at 1673cm^{-1}.In UV (λmax, logε) peaks are at 208 (4.7), 275(4.8), 335(4.9), 372(4.0) suggest enone chromophore . In the ^{1}Hnmr of **2a** the olefinic proton (H-3a) appeared at δ 8.00 (d, *J*=1.0Hz) assignable to E-configuration where as Z isomer arylidene proton signal is reported to resonate at δ 6.0[9]. The 2-CH_2 appeared as doublet at δ 5.46(*J*=1.0 Hz), the aromatic protons resonated at δ 8.05 (d, *J*=9.0 Hz, H-5), δ

6.65 (dd, J=9.0 Hz, 2.5 Hz, H-6), δ 6.40 (d, J=2.5Hz, H-8) the C-7 methoxyl protons appeared as singlet at δ 3.85. The thiophenyl protons appeared as multiplet at δ 7.15-7.60

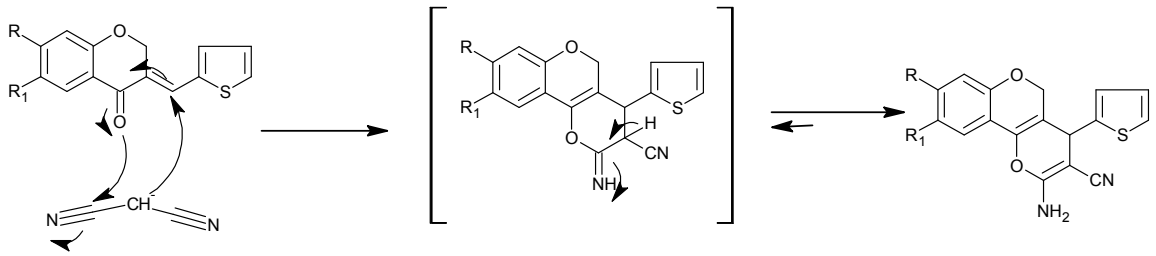
Synthesis of 2-amino-4-thiophenyl-4H,5H-[1]-benzopyrano[4,3-b]-pyran-3-carbonitriles 3a-e.

Treatment of the 3-thiophenylidene-4-chromonone **2a-e** with malononitrile in the presence of piperidine afforded 2-amino- 4-thiophenyl 4H,5H-[1]-benzo pyrano[**4,3-b]**-pyran-3-carbonitriles **3a-e (Scheme-1).** In its IR (KBr) of **3a** showed the cyano and amino peaks at 2200 and 3400cm^{-1}. In the ^{1}Hnmr of **3a,** the NH_2 resonated as broad singlet at δ 5.35, a two proton singlet at δ 4.80 assigned to H-5, while H-4 appeared as a singlet at δ 4.50, H-10 and the aromatic protons appeared at δ 7.52 (d, *J*=2.5Hz, C_7- H), δ 6.75(dd, H, *J*=9.0Hz, 2.5Hz, H-9), δ 8.35(d, H, *J*=9.0Hz, H-10) , and the C-8 methoxy protons appeared at δ 3.85 as singlet. The thiophenyl protons resonated as a multiplet in the region δ 7.10-7.30.



Scheme-1

The mechanism for the formation of **3a-e** is shown in (**Scheme -2)**, the reaction of malononitrile with 3-thiophenylidene-4-chromonones **2a-e** proceed by the Michael addition. Attack of the malononitrile anion at the activated double bond of **2a-e** is followed by tandem cyclisation gives the intermediate **4** which tautomerises to substituted 2-amino-4-thiophenyl-4H,5H-[1]-benzo pyrano[4,3-b]-pyran-3-carbonitriles **3a-e**.



4

Scheme-2

Antibacterial activity

compounds **2a-e**, 3**a-e** were tested *in vitro* for their antibacterial activity against Gram-positive bacteria *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 2453) by using Dimethylsulphoxide (DMSO) as solvent control. All the compounds were screened at **1mg/mL** concentration. Compounds **2a** and **3d** showed good activity against Gram-negative bacteria only i.e., *E. coli* (14.4-15.0 mm) and *P. aeruginosa* (13.5-15.0 mm) respectively. The remaining compounds exhibited moderate to low antibacterial activity against both Gram-positive (8.1-13.1mm) and Gram-negative (8.6-14.8 mm) bacteria respectively. The results are recorded in **Table 1**. Streptomycin(16.4-19.6 mm) used as standard for comparison of antibacterial activity.

Table.1. Antibacterial activity of compounds (**2a-e** & **3a-e**).

Compound	Diameter of zone of growth inhibition (mm)			
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
2a	12.2	10.7	14.8	13.6
2b	10.2	9.6	12.6	9.8
2c	9.0	8.8	11.1	9.7
2d	10.7	12.8	11.9	10.6
2e	11.3	10.9	10.8	9.6
3a	8.1	-	9.7	11.9
3b	8.1	9.2	9.6	9.9
3c	8.8	9.1	12.5	10.3
3d	-	12.2	10.9	14.4
3e	9.5	13.1	9.1	8.9
Streptomycin	16.9	19.6	16.4	16.9

Conclusion

The reaction of 3-thiophenylidene-4-chromonones **2a-e** with malononitrile is a new one pot and facile route to the densely functionalized 2-amino-4-thiophenyl-4H,5H-[1]-benzo pyrano[4,3-b]-pyran-3-carbonitriles **3a-e**. All the compounds are purified without lengthy chromatographic methods. Except **2a & 3d**, all the other compounds have shown low to moderate antibacterial activity.

Experimental Section

All melting points were determined on a Polmon digital melting point apparatus (Model No. MP-96) and are uncorrected. IR spectra were recorded on a Schimadzu 435 instrument using KBr and UV spectra were recorded on a Schimadzu UV-VIS 1601 spectrophotometer. The ^{1}H NMR (200 MHz) were recorded on a Bruker Spectrometer in $CDCl_3$ using TMS as internal standard (chemical shifts in δ ppm). EIMS spectra were obtained at 70ev.

Antibacterial study

The antibacterial activity was determined by disc diffusion method[10]. The compounds dissolved in DMSO (1 mg/mL) in which the Watman paper No. 1 paper disks (6 mm diameter) impregnated, dried under sterile flow box and put on an agar plates inoculated on nutrient agar plates previously seeded with test bacteria. The plates were incubated at 37°C for bacteria (18-24 hours) and examined for the zones of inhibition. Streptomycin used as positive and negative control. The organisms *B. subtilis* MTCC 121, *S. aureus* MTCC 96, *E. coli* MTCC 739, *P. aeruginosa* MTCC 2453 used for antimicrobial assays. The experiment was performed in triplicates.

Compounds **1a-e** were prepared by reported procedure [11].

General Procedure for the synthesis of 3- thiophenylidene -4-chromonones 2a-e: An ice cold solution of 4-chromonone **1a-e (**10mmol) and thiophene-2-carbaldehyde (10mmol) are taken in acetic acid(30ml) and treated with conc.HCl and set aside for 24hrs at 0^{o}C . The products **2a-e** separated from solution were collected and decomposed with cold water and recrystallized from aq.ethanol.

2a:m.p-206^{o}C, yield-92%, IR(KBr) 1673cm^{-1}(CO), UV-λmax (logε) 208(4.7), 275(4.8), 335(4.9), 372(4.0); ^{1}H NMR(200MHz- $CDCl_3$) δ 3.85(s, OCH_3), 5.46, (d, *J*=1.0Hz, 2-OCH_2), 6.40(d, *J*=2.5Hz, H-8), 6.65(dd, *J*=2.5Hz, 9.0Hz, H-6), 7.15-7.60(thiophenyl protons), 8.00(d, *J*=1.0Hz, H-3a), 8.05(d, *J*=9.0Hz, H-5); MS: *m/z* $M^{+\cdot}$ 272 Anal, calcd for $C_{15}H_{12}O_3S$, C-66.20%, H-5 42% found C-66.17%, H-4.45%.

2b:m.p-150^{o}C, yield-72%, IR(KBr)1675cm $^{-1}$ (CO), UV-λmax (logε) 209(4.7), 275(4.8), 336(4.9), 372(4.0); ^{1}H NMR (200 MHz $CDCl_3$) δ 5.45 (d, *J*=1.0Hz, 2-OCH_2), 6.93(d, *J*=9.0Hz, H-8), 7.40(dd, *J*=2.0Hz, 9.0Hz, H-7), 7.15-7.60(*m*, thiophenyl protons), 7.95(d, *J*=2.0Hz, H-5), 7.98(d, *J*=1.0Hz, H-3a), MS: *m/z* $M^{+\cdot}$ 276. Anal, calcd for $C_{14}H_9O_2SCl$, C-68.70%, H-3.70% found C-68.69%, H-3 69%

2c:m.p-215^{o}C, yield-77% IR(KBr)1674cm^{-1}(CO), UV-λmax (logε) 208(4.8), 275(4.9), 335(4.0), 371(4.0); ^{1}H NMR (200 MHz $CDCl_3$) δ 5.43 (d, *J*=1.0Hz, 2-OCH_2), 6.60(dd, *J*=2.5Hz, 9.0Hz, H-8), 6.75(dd, *J*=2.5Hz, H-7), 7.20-7.50(m, thiophenyl protons) 7.80(d, *J*=2.5Hz, H-5), 8.00(d, *J*=1.0Hz, H-3a); MS: *m/z* $M^{+\cdot}$320. Anal, calcd for $C_{14}H_9O_2BrS$, C-52.34%, H-2.84%, found C-52.33%, H-2.83%

2d:m.p-250^{o}C, yield-72.5%, IR(KBr)1673cm^{-1}(CO), UV-λmax (logε) 207(4.7), 276(4.8), 356(4.9), 372(4.0); ^{1}H NMR(200MHz $CDCl_3$) δ 5.43 (d, *J*=1.0 Hz, 2-OCH_2), 6.80(d, *J*=2.5Hz, H-8), 6.90(dd, *J*=9.0, 2.5Hz, H-6), 7.10-7.60(m, thiophenyl protons), 7.80(d, *J*=1.0Hz, H- 3a), 7.90(d, *J*=9.0Hz, H-5). MS: *m/z* $M^{+\cdot}$ 276. Anal,calcd for $C_{14}H_9O_2SCl$, C-68.69%, H-3.27% found C-68.68%, H-3.26%.

2e:m.p-180^{o}C yield-70% , IR(KBr)1674cm^{-1}(CO), UV-λmax (logε) 210(4.7), 280(4.8), 335(4.7), 374(4.1); ^{1}H NMR(200MHz $CDCl_3$) δ 5.43 (d, *J*=1.0 Hz, 2-OCH_2), 6.91(d, *J*=2.0Hz, H-8), 7.41(dd, *J*=9.0, 2.0Hz, H-6), 7.15-7.50(m, thiophenyl protons), 7.94(d, *J*=9.0Hz, H-5), 7.97 (d, *J*=1.0 Hz, H- 3a). MS: *m/z* $M^{+\cdot}$ 320. Anal, calcd for $C_{14}H_9O_2BrS$, C-52.34%, H-2.84%, found C-52.33%, H-2.83%

General procedure for the synthesis of 2- amino-4-thiophenyl-4H, 5H-[1]-benzo pyrano [4,3-b]-pyran-3-carbonitriles 3a-e

3-thiophenylidene-4-chromonones **2a-e**(10mmol) and malononitrile(10mmol) were dissolved in ethanol(20ml)and piperidine(3ml) was added and the reaction mixture was stirred at room temperature for 24hrs. The solvent was removed and the products **3a-e** were filtered and dried, recrystallized from aq ethanol as yellow crystals.

3a:m.p-225^{o}C, yield-53.2% IR-2200cm^{-1}(CN), 3400 cm^{-1} (NH_2); ^{1}H NMR (200 MHz $CDCl_3$) δ 3.85(s, OCH_3), 4.50(bs, H-4), 4.80(s, 5-OCH_2), 5.35(bs, NH_2), 6.75(dd, *J*=9.0Hz, 2.5Hz, H-9), 7.10-7.30(m, thiophenyl protons), 7.52(d, *J*=2.5Hz, H-7), 8.35(d, *J*=9.0Hz, H-10). MS: *m/z* $M^{+\cdot}$ 338, Anal, calcd for $C_{18}H_{14}O_3N_2S$, C-63.92%, H-4.15%% found C-63.90%, H-4.14% N-8.28%;, N-8.27%.

3b:m.p-203^{o}C, yield-52% IR-2200cm^{-1}(CN), 3400 cm^{-1} (NH_2); ^{1}H NMR δ 4.30(bs, H-4), 4.76(s, 5-OCH_2), 5.25 (bs, NH_2), 7.02(d, *J*=10.0Hz, H-7), 7.10-7.30(m, thiophenyl protons), 7.64(dd, *J*=10.0Hz, 2.5Hz, H-8), 8.34(d, *J*=2.5Hz, H-10), MS: *m/z* $M^{+\cdot}$ 342, Anal, calcd for $C_{17}H_{11}O_2N_2SCl$, C-59.57%, H-3.22%, N-8.18%, found C-59.56%, H-3.21% N-8.17%.

3c:m.p-227^{o}C, yield-64.5% IR-2210cm^{-1}(CN), 3405 cm^{-1} (NH_2); ^{1}H NMR δ 4.50(bs, H-4), 4.85(s, 5-OCH_2), 5.34 (bs, NH_2), 6.85(dd, *J*=10.0Hz, 2.5Hz, H-8), 7.10-7.30(m, thiophenyl protons) 7.65(d, *J*=10.0Hz, H-7), 8.47(d, *J*=2.5Hz, H-10), MS: *m/z* $M^{+\cdot}$ 354, Anal calcd for $C_{17}H_{11}O_2N_2SBr$, C-63.32%, H-3.10%, N-8.12%, found C-63.21%, H-3.09% N-8.10%.

3d:m.p-239^{o}C, yield-55% IR-2200cm^{-1}(CN), 3400 cm^{-1} (NH_2); ^{1}H NMR, δ 4.50(bs, H-4), 4.90(s, 5-OCH_2), 5.25 (bs, NH_2), 6.89(dd, *J*=10.0Hz, 2.5Hz, H-9), 7.10-7.30(m, thiophenyl protons), 7.67(d, *J*=2.5Hz, H-7), 8.25(d, *J*=10.0Hz, H-10). MS: *m/z* $M^{+\cdot}$ 342, Anal calcd for $C_{17}H_{11}O_2N_2SCl$, C-59.57%, H-3.23%, N-8.13%, found C-59.56%, H-3.22% N-8.12%.

3e:m.p-211^{o}C, yield-60% IR-2200cm^{-1}(CN), 3380 cm^{-1} (NH_2); ^{1}H NMR δ 4.31(s, H-4), 4.75(s, 5-OCH_2), 5.25 (bs, NH_2), 6.85(dd, *J*=10.0Hz, 2.5Hz, H-9), 7.10-7.30(m, thiophenyl protons), 7.61(d, *J*=2.5 Hz, H-7), 8.29(d, *J*=10.0 Hz, H-10). MS: *m/z* $M^{+\cdot}$ 354, Anal calcd for $C_{17}H_{11}O_2N_2SBr$, C-63.31%, H-3.9%, N-8.11%, found C-63.22%, H-3.1% N-8.11%.

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