Indian Journal of Chemistry
Vol. 58B, August 2019, pp. 916-920

Synthesis, characterisation and antimicrobial screening of some new thiazolyl chromones and pyrazoles

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Received 16 February 2018; accepted (revised) 2 May 2019

A series of substituted chromones and pyrazole derivatives have been synthesized from esterification of acid **1** with 2-hydroxy acetophenones **2** to give compounds **3** which is in turn converted in to β-diketones **4** in presence of excess of KOH by Baker-Venkatraman transformation. Acid catalysed cyclisation of β-diketones **4** yield a series of 2-substituted chromones **5**. 2-Substituted chromones **5** have been used to synthesise substituted pyrazole derivatives **6**. All the synthesised compounds have been characterised by spectral and analytical data. Chromones and pyrazoles have been evaluated for their antibacterial and antifungal activities.

Keywords: Baker-Venkatraman transformation, β-diketones, chromones, pyrazoles

In recent years it was found that microbial infections and drug resistivity of microbes have been increased enormously. Therefore it is necessary to develop a new and effective antimicrobial drug. The researcher's efforts have been made towards the designation of new agent. For designation of new agents heterocyclic molecules play important role because most of the heterocyclic compounds are biologically active. Chromones are found to be naturally occurring oxygen containing heterocyclic compounds and well known for their biological activities such as antitumor[1], antioxidant[2], antiinfective[3], antiallergic[4], antiinflammatory[5], anticancer[6], antiplatelate[7], antifungal[8] and antibacterial[9] activities. 3-formylchromones are important synthon for incorporating chromone moieties into heterocyclic system[10,11].

Pyrazole moiety is one of the most important biologically active heterocyclic compound. Pyrazole and its derivatives are associated with antibacterial[12] antifungal[13], antidiabetic[14], antiparasitic[15], anti-tubercular[16] and antiviral[17] activities (Figure 1 and Figure 2).

Thiazole is nitrogen and sulphur containing heterocyclic compound and found to be a structural fragment of naturally occurring vitamin, vitamin B1 (Thiamine). Thiazole derivatives are associated with wide range of biological activities including antibacterial[18], anticancer[19], anticonvulsant[20], antituberculousis[21], antifungal[22], antianaesthetic[23], antiinflamaratory[24] and antisedative[25]. Chlorinated heterocyclic compounds are found to be biological active and shows biological activities such as antioxidant[26], antiinflamaratory[26] and analgesic[26] (Figure 1).

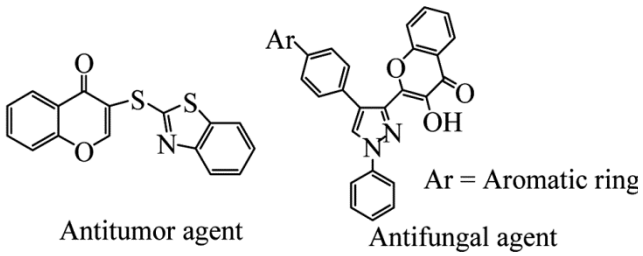


Figure 1

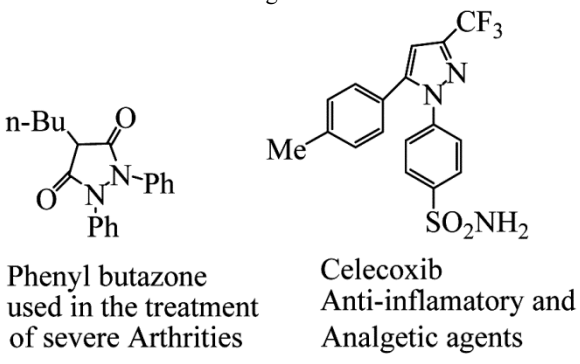
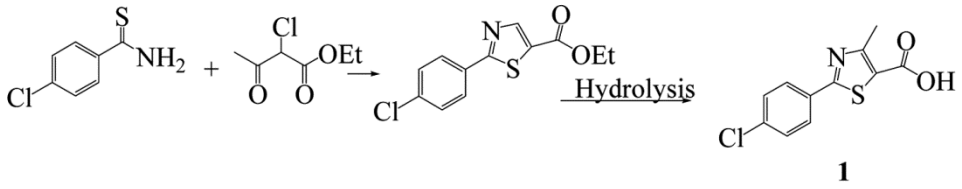


Figure 2

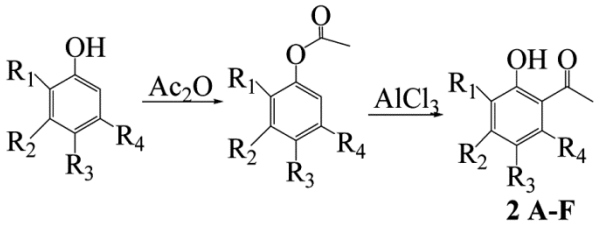
Promoted from this data, we synthesised a new series of thiozolyl chromones and pyrazoles and investigated for their antimicrobial activities.

Result and Discussion

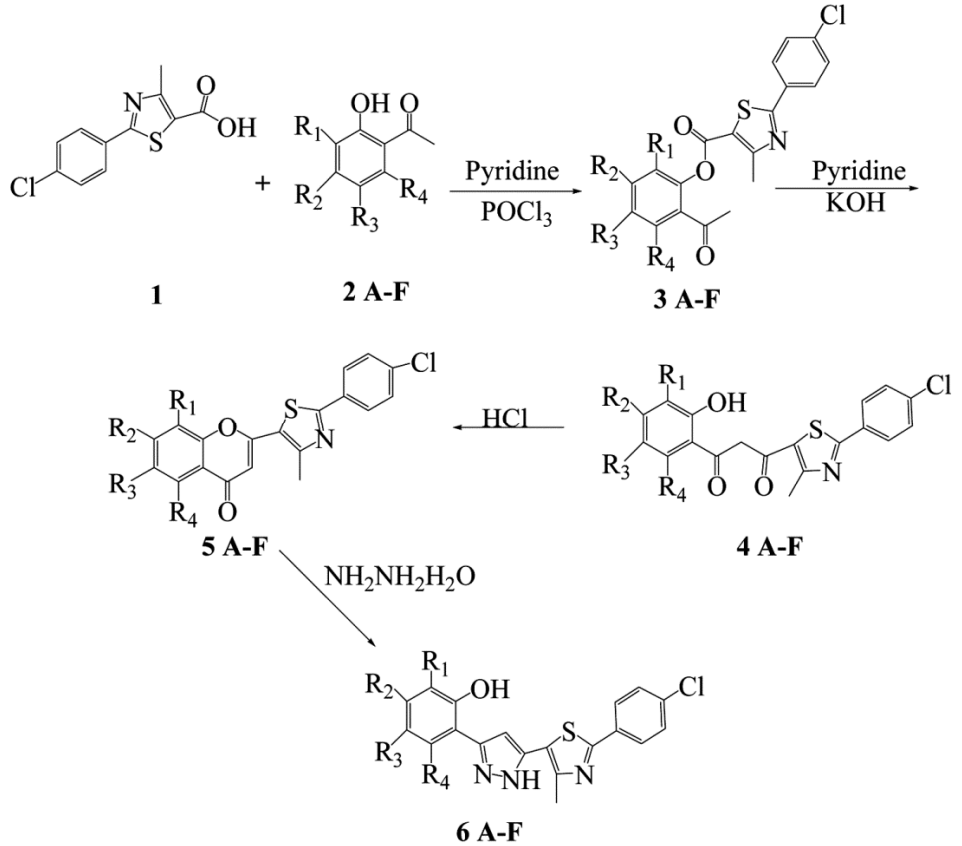
For the synthesis of target molecules, 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylic acid **1** and a series of substituted 2-hydroxyacetophenones **2** were used. Compounds **1** and **2A-G** were prepared by using well known literatures methods as shown in Scheme I and Scheme II. Esterification of acid **1** and 2-hydroxyacetophenones **2** results compounds **3A-G**. β-Diketones **4A-G** were obtained from compounds **3A-G** by stirring in pyridine and excess of KOH. Chromones **5A-G** was results from **4A-G** by intermolecular cyclisation in presence of conc. HCl. Pyrazoles **6A-G** were yielded by refluxing Chromones **5A-G** in hydrazine hydrate as shown in Scheme III. Physical



Scheme I



Scheme II



Scheme III

characterisation data of synthesised compounds is given in Table I. The ^{1}H NMR spectrum of **3C** showed two singlets at δ 2.58 and 2.74 for two methyl groups. Two doublet signals at δ 7.61 and 7.63 supported the presence of tetrasubstituted phenyl ring. The IR spectrum of **3C** showed 1736 and 1698 cm^{-1} bands for ester and ketone carbonyl stretching frequencies. The ^{1}H NMR spectrum of **4C** showed one singlet at δ 2.70 of methyl groups. Disappearance of one methyl signal from ^{1}H NMR spectrum supported the structure of **4C**. The IR spectrum of **4C** showed a band at 1735 cm^{-1} for carbonyl stretching frequency of ketone. The ^{1}H NMR spectrum of **5C** showed one singlet at δ 2.50 of methyl groups. The IR spectrum of **5C** showed a band at 1664 cm^{-1} for a conjugated carbonyl stretching frequency. The ^{1}H NMR spectrum of **6C** showed two signals at δ 10.60 and δ 13.40 confirm the presence of –OH & -NH protons indicating the presence of pyrazole ring in synthesised molecule. The IR spectrum of **6C** showed a band at 3350 cm^{-1} showed the presence of phenolic –OH group. Mass spectroscopy also supported for confirmation of formation of these compounds.

Table I — Physical characterisation data of synthesised compounds

Compd	R_1	R_2	R_3	R_4	Yield (%)	m.p.(°C)
3A	H	H	Me	H	66	168-170
3B	H	H	Cl	H	64	176-178
3C	Cl	H	C1	H	62	126-128
3D	H	H	Br	H	63	178-180
3E	H	H	C1	Me	61	148-150
3F	H	H	H	H	60	128-130
3G	H	H	H	Me	55	134-136
4A	H	H	Me	H	72	180-182
4B	H	H	C1	H	74	188-190
4C	C1	H	C1	H	70	182-184
4D	H	H	Br	H	76	252-254
4E	H	H	C1	Me	75	220-222
4F	H	H	H	H	78	218-220
4G	H	H	H	Me	80	210-212
5A	H	H	Me	H	67	186-188
5B	H	H	C1	H	64	180-182
5C	C1	H	C1	H	65	188-190
5D	H	H	Br	H	63	168-170
5E	H	H	C1	Me	66	198-200
5F	H	H	H	H	62	178-180
5G	H	H	H	Me	60	180-182
6A	H	H	Me	H	58	220-222
6B	H	H	C1	H	54	248-250
6C	C1	H	C1	H	52	258-260
6D	H	H	Br	H	53	218-220
6E	H	H	C1	Me	60	244-246
6F	H	H	H	H	56	234-236
6G	H	H	H	Me	58	238-240

Antimicrobial activity

An antimicrobial activity of synthesised compounds **5A-G** and **6A-G** was determined *in vitro* against four bacterial strains *Escherichia coli*, *Salmonella typhi*, *Bacillus subtilis* and *Staphylococcus aureus* maintained on nutrient agar plates at 37°C by agar well diffusion method. Plate containing 20 mL of nutrient agar was spread with 100 µl of culture. The wells were made in the agar cork boarer of width of 6 mm. The 100 µl of test compounds were loaded in the well along with ciprofloxine as positive control and DMSO as vehicle control. The plates incubated at 37°C for 24 hrs. Growth was evaluated visually by comparing a test plate with the control plates. All the experiments were performed in triplicates.

Similarly an antifungal activity of synthesised compounds **5A-G** and **6A-G** was determined *in vitro* against fungal strain-*Aspergillus niger* on sabouraud agar plates at 37°C by disc diffusion method. Plates containing 20 mL sabouraud agar spread with 0.1 mL of suspension of *Aspergillus niger* of 10^6 / mL of spores. Whatman filter paper disc soaked in solution of compounds (0.1 mg/ mL) was placed on plates along with Flucanazole as positive control and DMSO as a negative control. The plates were incubated at 37°C for 48 hrs. In this study results showed that except **5G** and **6G** no other compound shows antifungal activities.**5G** shows moderate and **6G** shows weak antifungal activity as shown in Table II.

Experimental Section

Melting points were determined by open capillary method and are uncorrected. The homogeneity of compounds was checked on silica gel TLC plates. IR spectra were recorded in KBr on a FT-IR spectrophotometer and mass spectra were recorded on a Q-TOF MS ES-3.84e3. ^{1}H NMR spectra on BRUKER AVANCE II 400 NMR spectrometer with DMSO-d_6 as a solvent and chemical shift (δ) are expressed in ppm using TMS as internal standard.

General procedures

2-Acetyl-4-methylphenyl-5-(4-chlorophenyl)-4-methylthiazole-2-carboxylate 3A

Equimolar quantities of compound **1** (0.01 mol) and compound **2** (0.01 mol) was dissolved in 10 mL of dry pyridine and the mixture were cooled to 0°C in

Table II — Results of antimicrobial activities of synthesised compounds

Synthesised Compd	Zone of inhibition in mm				
	E. coli	*S.typhi*	*B.subtilis*	*S.aureus*	*A.niger*
5A	15	13	13	13	–
5B	16	12	13	15	–
5C	14	15	14	13	–
5D	14	12	15	16	–
5E	17	15	15	15	–
5F	19	16	16	17	–
5G	18	15	16	16	8
6A	12	11	12	10	–
6B	12	12	13	11	–
6C	13	13	13	14	–
6D	15	13	12	13	–
6E	18	14	14	16	–
6F	16	15	15	14	–
6G	17	14	17	16	6
Ciprofloxin	20	18	20	18	–
Flucanazole	–	–	–	–	12

an ice bath. To this reaction mixture 0.01 mol $POCl_3$ was added with stirring maintaining the temperature below 5°C. After the complete addition of $POCl_3$, the reaction mixture was kept overnight and then poured over crushed ice. The resulting solid product thus obtained was filtered and washed with cold 1% NaOH solution followed by water. The desired product **3A** was purified by recrystallisation from ethanol. Compounds **3B-G** were prepared using the same method.

3C: Brown solid. IR (KBr): 3081, 2924, 1736, 1698, 1088 cm^{-1}; MS: *m/z* 440.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.61 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 8.08 (m, 3H, Ar-H), 8.13 (d, 1H, Ar-H). Anal. Calcd for $C_{19}H_{12}O_3Cl_3NS$: C, 51.78; H, 2.74; N, 3.18. Found: C, 51.75; H, 2.76; N, 3.16%.

3D: Brown solid. IR (KBr): 3074, 1728, 1682, 1049 cm^{-1}; MS: *m/z* 450.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 7.41 (d, 1H, Ar-H), 7.63 (m, 2H, Ar-H), 7.91 (dd, 1H, Ar-H), 8.09 (m, 2H, Ar-H), 8.16 (d, 1H, Ar-H). Anal. Calcd for $C_{19}H_{13}O_3ClBrNS$: C, 50.63; H, 2.91; N, 3.11. Found: C, 50.65; H, 2.92; N, 3.14%.

1-[5-(4-chlorophenyl)-4-methylthiazole-2-yl]-3-(2-hydroxy-5-methylphenyl) propane-1, 3-dione 4A

Compound **3A** (0.055 mol) was taken in 15 mL dry pyridine to this excess of powdered KOH was added with constant stirring. After complete addition of KOH the reaction mixture was stirred at R.T. for 3 hrs. Then the content was poured over crushed ice and acidified with conc. HCl. The resulting product was filtered and purified by recrystallisation from ethanol to get **4A**. Compounds **4B-G** were prepared using the same method.

4C: Yellow solid. IR (KBr): 3451, 2923, 1735, 1094 cm^{-1}; MS: *m/z* 440.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 6.46 (s, 1H, CO-CH_2), 7.54 (d, 2H, Ar-H), 7.65 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H), 7.96 (d, 2H, Ar-H), 11.26 (s, 1H, Ar-H) 14.03 (s, 1H, C=C-OH). Anal. Calcd. for $C_{19}H_{12}O_3Cl_3NS$: C, 51.78; H, 2.74; N, 3.18. Found: C, 51.76; H, 2.72; N, 3.20%.

4D: Yellow solid. IR (KBr): 3429, 2925, 1737, 1098 cm^{-1}; MS: *m/z* 450.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 6.40 (s, 1H, CO-CH_2), 7.47 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.89 (s, 1H, Ar-H), 7.99 (d, 2H, Ar-H), 11.28 (s, 1H, Ar-H), 13.76 (s, 1H, C=C-OH). Anal. Calcd. for $C_{19}H_{13}O_3ClBrNS$: C, 50.63; H, 2.91; N, 3.11. Found: C, 50.62; H, 2.93; N, 3.13%.

2-[5-(4-chlorophenyl)-4-methylthiazole-2-yl]-6-methyl-4*H*-chromen-4-one 5A

Compound **4A** (0.05 mol) was mixed with in 20 mL ethanol to this 1 mL conc. HCl was added. Reaction mixture was refluxed for 2 hr. After completion of reaction, reaction mixture was cooled and poured into crushed ice. The resulting product was filtered and purified by recrystallisation from ethanol to get **5A**. Compounds **5B-G** were prepared using the same procedure.

5C: Yellow solid. IR (KBr): 3076, 2923, 1664, 1094 cm^{-1}; MS: *m/z* 422.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.10 (s, 1H, CO-CH=C), 7.63 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.85 (s, 1H, Ar-H), 7.93 (d, 2H, Ar-H), 8.03 (s, 1H, Ar-H). Anal. Calcd for $C_{19}H_{10}O_2Cl_3NS$: C, 53.99; H, 2.38; N, 3.31. Found: C, 53.97; H, 2.40; N, 3.29%.

5D: Yellow solid. IR (KBr): 3078, 2924, 1653, 1094 cm^{-1}; MS: *m/z* 432.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.51 (s, 3H, CH_3), 6.70 (s, 1H, CO-CH=C), 6.82 (s, 1H, Ar-H) 7.40 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.81 (s, 1H, Ar-H), 7.93 (s, 1H, Ar-H). Anal. Calcd. for $C_{19}H_{11}O_2ClBrNS$: C, 52.74; H, 2.56; N, 3.24. Found: C, 52.97; H, 2.60; N, 3.26%.

2-[5-(5-[4-chlorophenyl]-4-methylthiazol-2-yl)-1*H*-pyrazol-3-yl]-4-methylphenol 6A

Compound **5A** (0.02 mol) and hydrazine hydrate (0.005 mol) were taken in ethanol and refluxed for 4 h. After completion of reaction, the reaction mixture was cooled to RT and poured over crushed ice and

neutralised with glacial acetic acid. The resulting product was separated by filtration and purified by recrystallisation from ethanol to get **6A**. Compounds **6B-G** were prepared using the same procedure.

6C: White solid. IR (KBr): 3350, 2922, 1091 cm^{-1}; MS: *m/z* 436.5 (M^+); ^1H NMR (DMSO-d_6): δ 2.63 (s, 3H, CH_3), 7.22 (s, 1H, Ar-H), 7.37 (s, 1H, Ar-H), 7.51 (d, 2H, Ar-H), 7.83 (s, 1H, Ar-H), 7.93 (s, 2H, Ar-H), 10.60 (bs, 1H, Ar-OH), 13.40 (bs, 1H, N-H), Anal. Calcd. for $C_{19}H_{12}OCl_3N_3S$: C, 52.25; H, 2.77; N, 9.62. Found: C, 52.24; H, 2.75; N, 9.60%.

6D: White solid. IR (KBr): 3442, 2922, 1091 cm^{-1}; MS: *m/z* 446.5 (M^+); ^1H NMR (DMSO-d_6): δ 2.65 (s, 3H, CH_3), 6.92 (d, 1H, Ar-H), 7.10 (s, 1H, Ar-H), 7.29 (dd, 1H, Ar-H), 7.51 (d, 2H, Ar-H), 7.91-7.95 (m, 3H, Ar-H), 10.69 (bs, 1H, Ar-OH), 13.19 (bs, 1H, N-H). Anal. Calcd. for $C_{19}H_{13}OClBrN_3S$: C, 51.08; H, 2.93; N, 9.41. Found: C, 51.10; H, 2.95; N, 9.45%.

Acknowledgement

The authors are thankful to P.G. Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar and P.G. Department of Chemistry, New Arts, Commerce and Science College, Parner, Ahmednagar for providing chemicals and also thankful to the Management of Anekant Education Society, Baramati for constant encouragement and providing necessary research facilities, YCIS College, Satara for providing antimicrobial activities of synthesised compounds and to the Directors, SAIF and CIL, Panjab University, Chandigarh for providing spectral data and analytical data.

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