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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2019, Vol. 35, No.(1):
Pg. 481-484

Brief Communication

Synthesis and Antibacterial Screening of Novel Thiazolyl Pyrazole and Benzoxazole

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http://dx.doi.org/10.13005/ojc/350164

Received: June 18, 2018; Accepted: December 10, 2018)

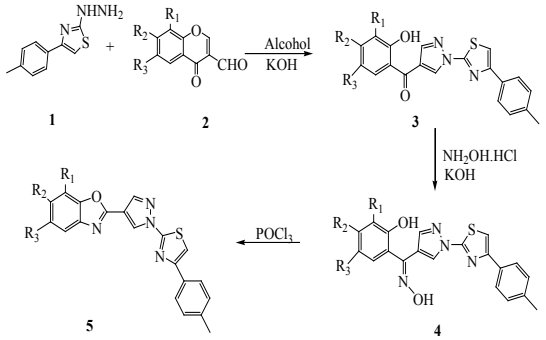
ABSTRACT

A new series of (2-hydroxyphenyl)(1-(4-p-tolylthiazol-2-yl)-1*H*-pyrazol-4-yl)methanone 3a-g, 2[(E)–{1-[4-(p-tolyl)-1, 3-thiazol-2-yl)]-1*H*-pyrazol-4-yl} (hydroxyimino)methyl]phenol 4a-g and 2-(1-(4-p-tolylthiazol-2-yl)-1*H*-pyrazole-4-yl)benzo[*d*]oxazole 5a-g have been synthesised. These synthesised compounds have been characterised by the spectral, analytical data and scanned for their antibacterial activities.

Keywords: Thiazole,3-formylchromone, Pyrazole, Benzo[*d*]oxazole.

INTRODUCTION

The introduction of heterocyclic moieties found in molecules have advantage in drug discovery and development because of its broad range of biological activities. Thiazole and its derivatives show biological activities such as anti-inflammatory[1], analgesic[2], antimicrobial[3,4], antioxidant[5], antitumor[6,7], anticonvulsant[8]. 3-formylchromone and its derivatives are known to associate in organic synthesis[9] and showing biological activities include antitumor[10], antibacterial[10], antitubulin[11], anti-helicobacter pylori[12], antiallergic[13], antioxidant[14], topoisomerase I inhibitor[15]. Pyrazole containing heterocyclic molecules are associated with wide range of biological activities such as antimicrobial[16], anticancer[17], antifungal[18], anti-inflammatory[19], antitumor[20], and anti-anxiety[21]. Benzoxazoles derivatives are found to be associated with anticancer[22], antimicrobial[23], HIV-1 reverse transcriptase Inhibitor Activity[24], inhibitors of lysophosphatidic acid acyltransferase-beta[25], anti-inflammatory[26], analgesic[26], antibacterial[27], antifungal[27], anticancer[28] activities. As a part of our interest in heterocyclic molecules have a extensive variety of biological activities and that have been explored for developing pharmaceutically important molecules, we here in report the synthesis of a set of new series of thiazolyl pyrazoles and benzoxazoles and their antibacterial activities.



Scheme 1

Table1: Physical characterisation of synthesised derivatives

Derivatives	R_1	R_2	R_3	Yield(%)	m.p.(°C)
3a	H	H	Me	62	220-222
3b	H	H	Cl	64	230-232
3c	H	Me	H	60	236-238
3d	H	Me	Cl	68	204-206
3e	H	H	H	61	186-188
3f	H	H	Br	63	228-230
3g	Cl	H	Cl	65	210-212
4a	H	H	Me	58	232-234
4b	H	H	Cl	54	246-248
4c	H	Me	H	55	192-194
4d	H	Me	Cl	60	250-252
4e	H	H	H	52	214-216
4f	H	H	Br	56	206-208
4g	Cl	H	Cl	64	202-204
5a	H	H	Me	67	232-234
5b	H	H	Cl	54	196-198
5c	H	Me	H	55	202-204
5d	H	Me	Cl	53	240-242
5e	H	H	H	56	224-226
5f	H	H	Br	52	228-230
5g	Cl	H	Cl	54	244-246

EXPERIMENTAL

All the chemicals were from Sigma – Aldrich and used without any purification. Melting Points of synthesised compounds were taken in open capillary tubes and uncorrected. IR spectra were obtained in KBr pallet on a FT-IR spectrophotometer and Mass spectra were recorded on a Q- TOF MS ES-3.84e3. ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer with DMSO-d_6 as a solvent and using TMS as internal standard. Chemical shift (δ) values are expressed in ppm.

(2-hydroxyphenyl)(1-(4-p-tolylthiazol-2-yl)-1*H*-pyrazol-4-yl)methanone 3

Equimolar mixture of thiazolyl hydrazine 1 (0.01 mol) and 3-formyl chromone 2 (0.01 mol) in ethanol were refluxed for 45 min, hydrazone derivative was obtained. Further, refluxing continues for 4-5 h by addition of 10 ml 15% potassium hydroxide. After completion of reaction the content was cooled, poured into ice and then neutralised by using c. HCl, solid pyrazolyl methanone derivative 3a produced. Then it was filtered and recrystallised from ethyl alcohol. The compounds 3b-g were synthesised by the same procedure.

3d. IR : 3105, 1654, 1610, 1106 cm^{-1}; Mass: m/z 409.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 6H, Ar-CH_3), 6.99 (s, 1H, Ar-H), 7.24 (d, 2H, Ar-H), 7.60 (s, 1H, Ar-H), 7.81 (s, 1H, Ar-H), 7.87 (d, 2H, Ar-H), 8.23 & 8.96 (s, 2H, Pyrazole), 10.88 (s, 1H, Ar-OH); Elemental analysis- Calculated. $C_{21}H_{16}O_2N_3S$ Cl: C, 61.53; H, 3.93; N, 10.25. Found: C, 61.55; H, 3.91; N, 10.27 %.

2[(E)–{1-[4-(p-tolyl)-1, 3-thiazol-2-yl)]-1H-pyrazol-4-yl}(hydroxyimino)methyl]phenol 4

To a solution of pyrazolyl methanone 3 (55 mmol) in ethanol, 15 ml 25% potassium hydroxide in water was added at about 0-4°C followed by hydroxylamine hydrochloride (1. 2 mol) in heaps. Once the the addition was complete, continues stirring for 4 h at room temperature. After reaction completion, content was poured into ice water and neutralised with acetic acid, solid thiozole anchored pyrazolyl oxime 4a separated. It was filtered and recrystallised from ethyl alcohol. The compounds 4b-g were synthesised by same procedure.

4d. IR : 3085, 1612, 1110 cm^{-1}; Mass: m/z 424.5 (M^+); ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 6.89 (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.24 (d, 2H, Ar-H), 7.66 (s, 1H, Ar-H), 7.82 (m, 3H, Ar-H), 8.88 (s, 1H, Ar-H), 9.98 (s, 1H, N-OH), 11.88 (s, 1H, Ar-OH); Elemental analysis- Calculated: $C_{21}H_{17}O_2N_4SCl$: C, 59.36; H, 4.03; N, 13.19. Found: C, 59.35; H, 4.05; N, 13.17%.

2-(1-(4-p-tolylthiazol-2-yl)-1*H*-pyrazole-4-yl) benzo[*d*]oxazole 5

The thiozolyl oxime 4 (5mmol) in 5 ml $POCl_3$ was taken in round bottom flask and refluxed for about 4 hour. After completion of reaction, cooled content was poured into ice and neutralised with 2% sodium hydroxide, solid gets separated. Then it was filtered and recrystallised from alcohol to afford oxazole 5a. Compounds 5b-g was synthesised by same method.

5d. IR : 1638, 1241, 1110 cm^{-1}; Mass: m/z 406.5 (M^+); ^1H NMR (DMSO-d_6): δ 2.36 (s, 3H, Ar-CH_3), 2.50 (s, 3H, Ar-CH_3), 7.30 (d, 2H, Ar-H), 7.82 (s, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 7.95 (d, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 8.58 & 9.36 (s, 2H, Ar-H); Elemental analysis- Calculated: $C_{21}H_{15}ON_4SCl$: C, 61.99; H, 3.72; N, 13.77. Found: C, 61.97; H, 3.74; N, 13.79 %.

Antibacterial activity

An antibacterial activity of synthesised compounds 3a-g, 4a-g and 5a-g were determined *in vitro* against two bacterial species *E. coli* and *B. subtilis.* By using agar well diffusion method, bacterial species were cultured on nutrient agar plates at 37°C. 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 amphicilin as positive control and DMSO as vehicle control. The plates incubated at 37°C for 24 hours. Growth was evaluated visually by comparing a test plate with the control plates. The figures in Table-II indicates inhibition zone in mm and these are the mean of triplicate assays.

Table 2: Results of antibacterial activities of synthesised compounds

Synthesised compounds	Inhibition zone in mm	
	Bacillus subtilis	*Escherichia coli*
3a	11	13
3b	9	14
3c	11	15
3d	12	15
3e	15	16
3f	13	10
3g	12	12
4a	13	14
4b	10	15
4c	12	14
4d	11	16
4e	11	16
4f	11	9
4g	13	14
5a	14	11
5b	12	16
5c	13	13
5d	13	14
5e	10	16
5f	12	14
5g	14	9
Amphicilin	16	17

RESULT AND DISCUSSION

Synthesised compounds 3a-g were obtained from the thiazole anchored molecule 1 and 3-formyl chromone 2. The yield of 3a-g compounds were in the range of 60-70%.The FTIR spectra of 3d shown peak at 3105 and 1654 cm^{-1} indicated the presence of Ar-OH and C=O groups in molecule. Whereas, the NMR spectra of 3d show the two singlets at δ 2.37 & 10.88 indicated the presence of Ar-CH_3 and Ar-OH.The compounds 4a-g were obtained from the compounds 3a-g and hydroxylamine hydrochloride by stirring at room temperature, practical yield of 4a-g compounds were in the range of 55-65%. From the FTIR spectra of 4d, the appearance of peak at 3085 cm^{-1} indicated the presence of Ar-OH and the disappearance of peak at 1654 cm^{-1} shown the absence of C=O group. The NMR spectra of 4d shown one singlet at δ 9.98 indicated the presence of –OH group of oxime. The compounds 5a-g were obtained from the refluxing the compounds 4a-g in $POCl_3$, yield in the range of 50-60%. The disappearance of IR peak at 3085 cm^{-1} shown the absence of Ar-OH in 5d. In the NMR spectra of 5d, absence of two singlet at δ 9.98 and 11.88 of N-OH & Ar-OH, confirmed the formation of compound 5d. Mass spectroscopy also supported for the formation of 3a-g, 4a-g and 5a-g compounds. Physical characterised data of synthesised compounds are given in the Table-1. The antibacterial activities of synthesised compounds are summarised in the Table–2. The figures indicate the zone of inhibition in mm. From the results it is apparent that among synthesised compounds 3e, 4g and 5b have shown good antibacterial activities.

ACKNOWLEDGEMENT

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

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