ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 10, pp.59721-59724, October, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF PYRANOPYRAZOLE BASED TETRAZOLES USING GLYCEROL AS GREEN SOLVENT

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ARTICLE INFO

Article History:
Received 20th July, 2017
Received in revised form
27th August, 2017
Accepted 10th September, 2017
Published online 31st October, 2017

Key words:

Pyranopyrazoles, Tetrazoles, Glycerol, Antibacterial, Green synthesis.

ABSTRACT

Pyranopyrazoles are valuable heterocyclic compounds in which pyran and pyrazole moiety coexist in same molecule. Pyranopyrazole derivatives are significant pharmacophores which are associated with broad range of biological applications. Pyrano(2,3-c) pyrazole derivatives show many bioactivities such as antimicrobial, insecticidal, anti-inflammatory activities and molluscicidal activity. But the production of such molecules required harsh reaction conditions and costly catalyst. So, in the present world reactions mediated with green protocols always attract much attention. In this report we synthesize some pyranopyrazole based tetrazoles using glycerol as clean and green solvent. The targeted compounds were evaluated for their anti-microbial activity and it was observed that pyranopyrazoles linked with tetrazoles exhibit potent antibacterial activity as compared to their starting analogues.

Citation: Manvinder Kaur and Harvinder Singh Sohal, 2017. "Synthesis and antimicrobial evaluation of Pyranopyrazole based Tetrazoles using glycerol as green solvent", *International Journal of Current Research*, 9, (10), 59721-59724.

INTRODUCTION

Synthesis of new class of heterocyclic compounds always attracted much attention for the researchers but the present methodologies are quite expensive due to the use of costly starting materials, solvent system, catalysts and reaction conditions. Therefore, production of desired compounds using inexpensive starting materials and green methodology is the main interest of the researchers. The development of green methodologies with the choice of suitable solvents from renewable resources has gained much interest in recent years (Handy, 2003; Leitner, 2007; Horváth, 2008; Giovanni *et al*., 2006; Clark, 1999). With this concern, use of water has attracted much attention (Simon and Li, 2012; Butler and Coyne, 2010; Chanda and Fokin, 2009; Li, 2007; Li, 2005; Li, 1993), however water based processes are still subject to limitations due to solubility problems of highly hydrophobic substrates. On the other hand, excellent solvent properties like low toxicity, biodegradability, low- flammability, long liquid range, low vapor pressure and solubility of polar organic compounds made the glycerol an excellent option to use as solvent for organic synthesis (Pagliaro and Rossi, 2008). Further with the present emphasis and increasing demand of biodiesel, which is responsible for the excess production of glycerol as by-product, triggered the discovery of processes that use glycerol for the synthesis of value added chemicals, as reaction medium and for other applications (Pagliaro *et al*., 2007; Corma *et al*., 2007; Armaroli *et al*., 2007; Jerome *et al*., 2008; Zhou *et al*., 2008; Behr *et al*., 2008; Bachhav *et al*., 2011). In addition, pyranopyrazoles are important class of heterocyclic chemistry. Compounds containing pyranopyrazole scaffold are biological active and have applications as pharmaceutical ingredients and biodegradable agrochemicals (Junek and Aigner, 1973; Wamhoff *et al*., 1993; Tacconi *et al*., 1980; Sharanin *et al*., 1983; El-Tamany *et al*., 1999). Pyrano(2,3-c)pyrazole derivatives possess wide range of bioactivities (Ismail *et al*., 2003; Zaki *et al*., 2006; Abdelrazek *et al*., 2006; Abdelrazek *et al*., 2007). These compounds are known to have applications in screening kit for Chk1 kinase inhibitor (Foloppe *et al*., 2006; Kimata *et al*., 2007) and also used as photoactive material (Armetso *et al*., 1989). By considering the useful biological activities related to pyranopyrazoles, extensive work has been carried out by numerous workers for the formation of new compounds having single or multi substituents but the preparations of the new tetrazoles bearing pyranopyrazoles have not been much explored in the literature. These aspects have prompted us to investigate the synthesis of a series of new pyranopyrazole based tetrazole molecules 2a-2i bearing different substituents. The main intention behind this research work was to examine the effect of the different substituents upon the synthesis and antimicrobial activity of these compounds 2a-2i.

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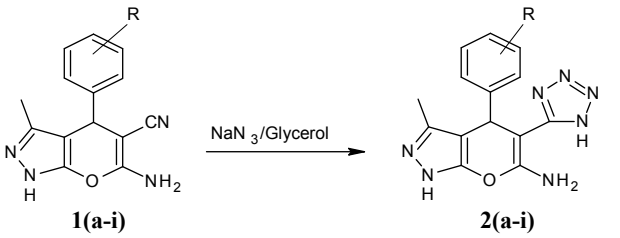

Scheme 1: Synthesis of 3-methyl-4-phenyl-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine **2(a-i)**

RESULTS AND DISCUSSION

Cyclization reaction of -C≡N group of pyranopyrazole **1a** with sodium azide were carried out in verity of solvent system, surfactant and surfactant based catalysts (Table-1). It was found that glycerol provided maximum yield in lesser time (Table-2). Further optimization of the reaction proved that glycerol forms appropriate cavity for the progress of the reaction and therefore acts as best solvent for such reactions and no further catalyst is required.

Table 1. Effect of solvent system and catalyst on the synthesis of 2a

S. No.	Catalyst	Solvent	[a]Yield of compound 2a (%)
1	SDS	Water	67
2	DBSA	Water	62
3	$Al(DS)_3$	Water	87
4	$(Hbim)BF_4$	-	48
5	$(Bbim)BF_4$	-	41

[a]Yield refer to combined amounts of different crops.

Table 2. Effect of temperature on the synthesis of 2a

Entry	Temperature[a] (°C)	Time (hr)	Yield[b] (%)
1	90	5	68
2	100	5	84
3	110	3	89
4	120	3	94

[a]Reaction carried in oil bath and temperature is controlled with thermometer.
[b]Yield refer to combined amounts of different crops.

The structure of the compound 2a was confirmed with the help of spectral techniques. In IR spectrum absorption at 3117 cm^{-1} represents the N-H stretching and absorption for NH_2 groups was observed at 3250 & 3372 cm^{-1}. In ^1H NMR spectrum, signal for five aromatic protons multiplet and one proton singlet for C*H* were observed at δ 7.18-7.48 and 4.66 respectively. The broad singlets resonating at δ 12.11 & 13.01 were given by N*H* protons and a singlet for CH_3 group was found to be present at δ 1.82. ESI-MS spectrum of 2a was also helpful to interpret its structure. Spectral data of 2a fully supports the structure assigned to it. Similarly the structural analysis of all the synthesized compounds 2b-2i was in accordance with obtained spectral data. To check the versatility of this process, we treated N-phenylpyrazole, ammonium acetate with different aldehydes and results are summarized in Table 2. Reactions proceed smoothly with aldehydes bearing electron withdrawing as well as electron donating substituents.

Antibacterial Evaluation

All the entitled compounds were screened for their antibacterial activity against three Gram-positive bacteria,

Table 3. Synthesis of pyranopyrazoles based tertrazole

Entry	Aldehyde (R)	Yield[a] (%)	Melting Point (°C)	R_f value[d]
2a	C_6H_5	94	251-252	0.77
2b	4-Cl C_6H_4	91	265-266	0.71
2c	3-NO_2 C_6H_4	89	240	0.76
2d	4-NO_2 C_6H_4	92	297-299	0.77
2e	4-Me C_6H_4	88	262-264	0.63
2f	3,4-Me C_6H_3	85	270-272	0.58
2g	4-OMe C_6H_4	84	227-229	0.63
2h	4-OH C_6H_4	82	248-249	0.74
2i	4-F C_6H_4	82	261-262	0.68

namely *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes* and three gram negative bacteria *Escherichia coli*, *Klebsellia pneumonia, Pseudomonas aeruginosa*. The potential of synthesized compounds were compared with a well-known antibiotic drug, Amoxicillin. Minimum inhibitory concentration of the screened compounds are depicted in Table 4. The results of antibacterial analysis revealed that presence of electron withdrawing groups at the phenyl ring attributed with maximum inhibition against all the tested bacterial strains as compared to electron donating groups attached to the phenyl ring. Interestingly, compounds containing single electron withdrawing group at the *para* position show greater inhibition at low MIC value (4 & 8 µg/mL) as compared to the *meta* substitution to the phenyl ring with moderate inhibition MIC value (8, 16 & 32 µg/mL). Further, it was also observed that phenyl ring substituted with two electron releasing groups (compound **2**) were completely inefficient against all the bacterial strains.

Table 4. MIC (µg/mL) of pyranopyrazoles based tertrazole 2a-2i

Entry	Gram (+ve) Bacteria			Gram (-ve) Bacteria		
	S. Aureus	*B. Subtilis*	*S. Pyogenes*	*E. Coli*	*K. Pneumonia*	*P. Aeruginosa*
2a	16	8	16	8	8	16
2b	16	16	16	8	16	32
2c	16	8	8	16	16	8
2d	4	4	8	4	4	8
2e	64	32	32	64	64	32
2f	128	128	128	256	128	256
2g	32	32	64	32	64	64
2h	32	16	32	16	16	8
2i	32	8	16	16	32	16
Amoxicillin	4	4	4	4	4	4

Experimental

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. ^1H-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 400 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The mass spectrum and IR spectra were recorded at LC-MS Spectrometer Model Q-ToF Micro Waters and Perkin-Elmer Spectrum II infra-red spectrophotometer, respectively. Elemental analyses (C, H, and N) were performed using a Thermo Scientific elemental analyzer. The reactions were monitored on thin layer chromatography (TLC) using silica gel-G. The spots were visualized by using iodine vapours.

Synthesis of 3-methyl-4-phenyl-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine 2a

In a conical flask compound 1a (0.01 mol), sodium azide (0.015 mol) were taken in glycerol (10 ml) and refluxed the

reaction mixture at 120 °C for the stipulated time (Table 2). After the completion of reaction (monitored by TLC), reaction mixture was cooled to room temperature and after adding 50 ml ice-cold water the solid was separated out. The compound was recrystalized from ethanol to afford compound 2a. Off white crystals. M.p.: 251-252 °C. FT-IR (KBr, ν, cm^{-1}): 3372, 3250, 3117, 2998, 1648, 1613. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.82 (s, 3H, CH_3), 4.66 (s, 1H, CH), 6.97 (s, 2H, NH_2), 7.18-7.48 (m, 5H, Ar-H), 12.11 (brs, 1H, NH), 13.01 (brs, 1H, NH). MS *m/z* 296 (M^+).

3-methyl-4-(4-chlorophenyl)-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2b)

White crystals. M.p.: 265-266 °C. FT-IR (KBr, ν, cm^{-1}): 3398, 3261, 3130, 2937, 2869, 1664, 1616. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.79 (s, 3H, CH_3), 4.59 (s, 1H, CH), 6.65 (s, 2H, NH_2), 7.23-7.45 (m, 4H, Ar-H), 11.90 (brs, 1H, NH), 13.01 (brs, 1H, NH. MS *m/z* 330 (M^+)

3-methyl-4-(3-nitrophenyl)-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2c)

Off white crystals. M.p.: 240 °C. FT-IR (KBr, ν, cm^{-1}): 3317, 3266, 3156, 2948, 2834, 1676, 1627, 1525, 1320. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.87 (s, 3H, CH_3), 4.88 (s, 1H, CH), 6.93 (s, 2H, NH_2), 7.58-8.21 (m, 4H, Ar-H), 12.09 (brs, 1H, NH), 13.08 (brs, 1H, NH). MS *m/z* 341 (M^+).

3-methyl-4-(4-nitrophenyl)-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2d)

White crystals. M.p.: 297-299 °C. FT-IR (KBr, ν, cm^{-1}): 3320, 3265, 3154, 2940, 2834, 1670, 1621, 1526, 1334, ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.90 (s, 3H, CH_3), 4.80 (s, 1H, CH), 6.90 (s, 2H, NH_2), 7.46 (d, 2H, Ar-H), 8.07 (d, 2H, Ar-H), 12.01 (brs, 1H, NH), 13.06 (brs, 1H, NH). MS *m/z* 341 (M^+).

3-methyl-4-(4-methylphenyl)-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2e)

Off white crystals. M.p.: 262-264 °C. FT-IR (KBr, ν, cm^{-1}): 3498, 3259, 3156, 2933, 2865, 1666, 1623. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.81 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.56 (s, 1H, CH), 6.62 (s, 2H, NH_2), 6.92-7.28 (m, 4H, Ar-H), 11.97 (brs, 1H, NH), 12.99 (brs, 1H, NH). MS *m/z* 310 (M^+).

4-(3,4-dimethylphenyl)-3-methyl-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2f)

Off white crystals. M.p.: 270-272 °C. FT-IR (KBr, ν, cm^{-1}): 3488, 3254, 3150, 2928, 2872, 1633, 1620. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.87 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.50 (s, 1H, CH), 6.60 (s, 2H, NH_2), 6.98 (s, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 7.11(d, 1H, Ar-H), 11.90 (brs, 1H, NH), 12.89 (brs, 1H, NH). MS *m/z* 324 (M^+).

3-methyl-4-(4-methoxyphenyl)-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-6-amine (2g)

Off white crystals. M.p.: 227-229 °C. FT-IR (KBr, ν, cm^{-1}): 3383, 3256, 3160, 2928, 2857, 1649, 1612. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.78 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.54 (s, 1H, CH), 6.88 (s, 2H, NH_2), 7.12-7.56 (m, 4H, Ar-H), 12.01 (brs, 1H, NH), 13.06 (brs, 1H, NH). MS *m/z* 326 (M^+).

4-[6-amino-3-methyl-5-(1*H*-tetrazol-5-yl)-1,4-dihydropyrano(2,3-*c*)pyrazol-4-yl]phenol (2h)

Light yellow crystals. M.p.: 248-249 °C. FT-IR (KBr, ν, cm^{-1}): 3480, 3369, 3256, 3178, 2928, 2860, 1649, 1612. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.88 (s, 3H, CH_3), 4.68 (s, 1H, CH), 6.80 (s, 2H, NH_2), 7.12 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 9.12 (s, 1H, OH), 11.96 (brs, 1H, NH), 12.88 (brs, 1H, NH). MS *m/z* 312 (M^+).

4-(4-fluorophenyl)-3-methyl-5-(1H-tetrazol-5-yl)-1,4-dihydropyrano (2,3-c)pyrazol-6-amine (2i)

White crystals. M.p.: 261-262 °C. FT-IR (KBr, ν, cm^{-1}): 3340, 3246, 3170, 2943, 2857, 1649, 1612. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.88 (s, 3H, CH_3), 4.78 (s, 1H, CH), 6.78 (s, 2H, NH_2), 6.98 (d, 2H, Ar-H), 7.16 (d, 2H, Ar-H), 11.88 (brs, 1H, NH), 12.56 (brs, 1H, NH). MS *m/z* 314 (M^+).

Antimicrobial evaluation

The *in vitro* antibacterial activity of all the synthesized compounds 2a-2i were evaluated against six bacterial strains (both gram positive and gram negative bacteria) *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441), *Streptococcus pyogenes* (MTCC 442), *Escherichia coli* (MTCC 443), *Klebsellia pneumonia* (MTCC 3384) and *Pseudomonas aeruginosa* (MTCC 424). Minimum Inhibition Concentration (MIC) of all the synthesized compounds 2a-2i was evaluated with help of serial tube dilution method (Behr *et al*., 2008) at several concentrations of 128, 64, 32, 16, 8, 4 µg/ml and all the stock solutions were prepared in DMSO by dissolving weighed amounts of compounds. Dilutions were made in nutrient broth medium to prepare various concentrations. Standard drug amoxicillin was used to evaluate MIC of the prepared compounds against the tested bacterial strains. All the bacterial strains were grown in nutrient broth media at 37˚C. The inoculated tubes were incubated for 24 hrs at 37˚C. The reference drug was also sustained at the similar conditions for comparison. The inhibition of the bacterial growth was determined by the appearance of turbidity after 24 hrs of incubation at 37°C. MIC of all the compounds is given in Table 4.

Conclusion

In the present procedure, tetrazoles are prepared in atom economy reaction between a cynide group and azide group under one-pot method with inherent flexibility and diversity. This method was efficacious to reduce labor, cost, waste production and also devoid of harsh reaction conditions. The target compounds were obtained in excellent yields (82-94%). Further, It had been observed that synthesized compounds showed a significant level of antibacterial activity. Compounds containing nitro group at *para*-position of phenyl ring attached to position-4 of pyranopyrazoles exhibit significant against the standard drug Amoxicillin where as presence of methyl groups show least activity. Further modification in the basic structure may lead to construct some potential chemotherapeutic agents in future.

Acknowledgements

Authors are highly thankful to Punjabi University, Patiala and Chandigarh University, Gharuan for providing all the necessary facilities during this research work.

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