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RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL STUDIES OF NEW PYRANOPYRAZOLE BASED BENZOXAZOLE DERIVATIVES

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ABSTRACT

A new series of pyranopyrazole based benzoxazole derivatives 2(a-h) were synthesized from reaction of compounds 1(a-h), o-aminophenol and carbon disulphide. The structures of the newly synthesized compounds have been established on the basis of rigorous analysis of their spectral data. The synthesized compounds were evaluated for their antimicrobial activities against selected bacterial strains using serial tube dilution method. It was observed that pyranopyrazoles based benzoxazole derivatives exhibit potent antibacterial activity as compare to their starting analogues.

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INTRODUCTION

Pyranopyrazoles are the valuable heterocyclic compounds in which five membered pyrazole ring is fused to a six membered pyran ring. These heterocycles are widely synthesized due to their important biological behaviours like ulcerogenic (Hafez, 2008), antimicrobial (Fathalla, 2009 and El-Assiery, 2004), antitubercular (Vaghasiya, 2008), antimalarial (Klein, 2009), antitumor (Naito, 1999; Abu-Hashem, 2010), antioxidant (Abu-Hashem, 2010), antiproliferative (Porba, 2006), antihypertensive, (Svetlik, 2009), hypnotic (Wang, 2004) and vasodilator (Li, 2005). Benzoxazoles are significant heterocyclic compounds which are known to possesses many biological applications (Kokubo, 2000; Yamato, 1992; Song, 2005; Kumar, 2002; Yildiz-Oren, 2004; Benazzou, 1995 and Evans, 1979). These derivatives have been also characterized as melatonin receptor agonists, (Sun, 2004), amyloidogenesis inhibitors, (Johnson, 2008) Rho kinase inhibitors (Sessions, 2008) and antitumor agents (Rida Samia, 2005). In addition to this, these heterocycles are recognized as an important scaffold in fluorescent probes (Taki, 2004). By considering the useful biological activities related to pyranopyrazoles and benzoxazole heterocycles, extensive work has been carried out by numerous workers for the formation of new compounds but the preparations of the new heterocycles bearing both pyranopyrazole and benzoxazole moieties within the same molecule have not been much explored in the literature. In view of these observations and in continuation of our research programme on the synthesis of six-membered heterocyclic compounds, (Sohal, 2014; Sohal, 2013 and Sohal, 2014), an in-depth study has been directed towards the design and synthesis of pyranopyrazole based benzoxazole compounds **2(a-h)** bearing different substituents. The main impetus behind these investigations was to examine the effect of different substituents on the synthesis and antimicrobial evaluations of the resultant heterocycles **2(a-h)**.

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EXPERIMENTAL

MATERIALS AND MATERIALS

All the chemicals used in this study were purchased from E. Merck, S. D. Fine Chem. Ltd., Mumbai and Sigma-Aldrich. The melting points were determined by using the open capillary method and are uncorrected. The Infrared (IR) spectra were scanned in KBr pellets on a Perkin Elmer RXIFT Infrared spectrophotometer. Both ^{1}H-NMR of the compounds were recorded on the Bruker Avance-II NMR Spectrometer at 400 MHz. The purity of the compounds was checked by TLC plates coated with silica gel (suspended in chloroform-methanol, 1:1) and iodine vapours were used as visualizing agent. The pyranopyrazoles **1(a-h)** were prepared according to the literature methods (Sohal, 2013) and their physical and spectroscopic data was found to be similar as reported earlier.

Synthesis of pyranopyrazoles 1(a-h): The compounds **1(a-h)** were prepared from the successive addition of hydrazine hydrate (1 mmol), ethylacetoacetate (1 mmol), aldehyde (1 mmol) and malononitrile (1 mmol) in glycerol (2 mL). The physical and spectral data of **1(a-h)** was found to be consistent as reported in literature (Sohal, 2013).

***Synthesis of pyranopyrazole based benzoxazole derivatives* 2(a-h):** A mixture of pyranopyrazoles (Sohal, 2013), **1(a-h)** (0.01mol), o-aminophenol (0.01 mol, 1.09 g) and carbon disulphide (0.1 mol, 8 ml) was heated in an oil bath at 150 ^{o}C for 8 hrs. TLC was used to check the progress of reactions (Hexane-Ethylacetate: 9:1). After the completion of reaction, excess solvent was evaporated. Rest reaction mixture was poured into ice to obtain solid products which were filtered, thoroughly washed with water and dried. The crude products thus obtained were crystallized from EtOH to yield pure compounds **2(a-h)**.

Synthesis of 5-(1,3-benzoxazol-2-yl)-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2a): Yellow, Yield 65%, m.p.: 120-122 °C; IR (KBr): υ_{max} cm^{-1}: 3390, 3216 (N-H$_2$), 3137 (N-H), 2940, 2836 (methylene C-H), 1590 (C=N) & 1248, 1069 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.30 (2H, brs, 1-N***H***), 7.45-7.01 (m, 9H, Ar-H), 6.95 (s, 2H, N***H$_2$***), 5.11 (2H, s, H-4), 1.80 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 367 (M+Na, 41%), 345 (M+1, 33%); Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C-69.76, H-4.68, N-16.27; Found: C- 69.71; H-4.70; N-16.21%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2b)

Light Yellow, Yield 62%, m.p.: 140-142 °C; IR (KBr): υ_{max} cm^{-1}: 3388, 3211 (N-H$_2$), 3128 (N-H), 2952, 2830 (methylene C-H), 1588 (C=N) & 1240, 1061 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.22 (2H, brs, 1-N***H***), 7.30-7.24 (m, 4H, benzoxazole ring), 7.16 (2H, d, J_o=7.8 Hz, Ar-H), 7.09 (2H, d, J_o=7.1 Hz, Ar-H), 6.88 (s, 2H, N***H$_2$***), 5.06 (2H, s, H-4), 1.86 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 401 (M+Na, 49%), 379 (M+1, 23%); Anal. Calcd. for $C_{20}H_{15}ClN_4O_2$: C-63.41, H-3.99, N-14.79; Found: C- 63.38; H-3.94; N-14.73%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2c)

Yellow, Yield 67%, m.p.: 170-172 °C; IR (KBr): υ_{max} cm^{-1}: 3364, 3210 (N-H$_2$), 3145 (N-H), 2938, 2837 (methylene C-H), 1598 (C=N) & 1249, 1086 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.21 (2H, brs, 1-N***H***), 7.32-7.25 (m, 4H, benzoxazole ring), 7.20 (1H, d, J_o=7.5 Hz, Ar-H), 7.11 (1H, brs, Ar-H), 7.08 (1H, t, J_o=6.9 Hz, Ar-H), 6.89 (1H, dd, $J_{m,o}$=2.0, 7.6 Hz, Ar-H), 6.84 (s, 2H, N***H$_2$***), 5.01 (2H, s, H-4), 1.94 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 401 (M+Na, 51%), 379 (M+1, 33%); Anal. Calcd. for $C_{20}H_{15}ClN_4O_2$: C-63.41, H-3.99, N-14.79; Found: C- 69.36; H-3.94; N-14.74%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2d)

Yellow, Yield 66%, m.p.: 160-162 °C; IR (KBr): υ_{max} cm^{-1}: 3372, 3214 (N-H$_2$), 3132 (N-H), 2946, 2854 (methylene C-H), 1592 (C=N) & 1236, 1072 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.24 (2H, brs, 1-N***H***),), 8.06 (2H, d, J_o=7.4 Hz, Ar-H), 7.78 (2H, d, J_o=7.7 Hz, Ar-H), 7.45-7.36 (m, 4H, benzoxazole ring), 6.90 (s, 2H, N***H$_2$***), 5.08 (2H, s, H-4), 1.92 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 412 (M+Na, 41%), 390 (M+1, 13%); Anal. Calcd. for $C_{20}H_{15}N_5O_4$: C-61.69, H-3.88, N-17.99; Found: C- 61.62; H-3.83; N-17.95%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2e)

Yellow, Yield 60%, m.p.: 148-150 °C; IR (KBr): υ_{max} cm^{-1}: 3360, 3216 (N-H$_2$), 3130 (N-H), 2940, 2839 (methylene C-H), 1596 (C=N) & 1238, 1074 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.27 (2H, brs, 1-N***H***), 8.01 (1H, d, J_o=7.5 Hz, Ar-H), 7.72 (1H, brs, Ar-H), 7.58 (1H, t, J_o=6.9 Hz, Ar-H), 7.47 (1H, dd, $J_{m,o}$=2.0, 7.6 Hz, Ar-H), 7.39-7.26 (m, 4H, benzoxazole ring), 6.91 (s, 2H, N***H$_2$***), 4.98 (2H, s, H-4), 1.84 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 412 (M+Na, 38%), 390 (M+1, 19%); Anal. Calcd. for $C_{20}H_{15}N_5O_4$: C-61.69, H-3.88, N-17.99; Found: C- 61.62; H-3.83; N-17.95%.

Synthesis of 4-[6-amino-5-(1,3-benzoxazol-2-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl]phenol (2f)

Yellow, Yield 68%, m.p.: 136-138 °C; IR (KBr): υ_{max} cm^{-1}: 3380, 3216 (N-H$_2$), 3142 (N-H), 2948, 2856 (methylene C-H), 1594 (C=N) & 1250, 1082 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.17 (2H, brs, 1-N***H***), 9.12 (1H, s, O***H***), 7.45-7.37 (m, 4H, benzoxazole ring), 7.14 (2H, d, J_o=7.4 Hz, Ar-H), 7.05 (2H, d, J_o=7.2 Hz, Ar-H), 6.90 (s, 2H, N***H$_2$***), 5.04 (2H, s, H-4), 1.89 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 383 (M+Na, 41%), 361 (M+1, 100%); Anal. Calcd. for $C_{20}H_{16}N_4O_3$: C-66.66, H-4.48, N-15.55; Found: C- 66.61; H-4.43; N-15.50%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2g)

Yellow, Yield 70%, m.p.: 148-150 °C; IR (KBr): υ_{max} cm^{-1}: 3372, 3221 (N-H$_2$), 3119 (N-H), 2944, 2850 (methylene C-H), 1592 (C=N) & 1242, 1068 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.20 (2H, brs, 1-N***H***), 7.40□7.32 (m, 4H, benzoxazole ring), 7.11 (2H, d, J_o=7.4 Hz, Ar-H), 7.02 (2H, d, J_o=7.2 Hz, Ar-H), 6.85 (s, 2H, N***H$_2$***), 5.01 (2H, s, H-4), 2.90 (s, 3H, -OC***H$_3$***), 1.90 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 397 (M+Na, 21%), 375 (M+1, 63%); Anal. Calcd. for $C_{21}H_{18}N_4O_3$: C-67.37, H-4.85, N-14.96; Found: C- 67.34; H-4.81; N-14.91%.

Synthesis of 5-(1,3-benzoxazol-2-yl)-3-methyl-4-(4-methylphenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (2h)

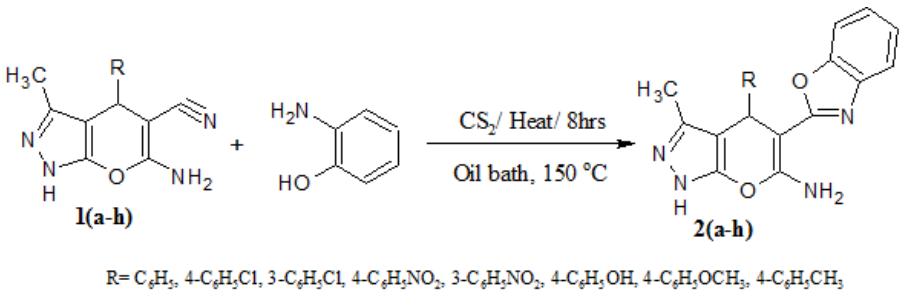
Yellow, Yield 62%, m.p.: 128-130 °C; IR (KBr): υ_{max} cm^{-1}: 3378, 3236 (N-H$_2$), 3124 (N-H), 2936, 2844 (methylene C-H), 1590 (C=N) & 1238, 1070 (C-O); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.20 (2H, brs, 1-N***H***), 7.46-7.35 (m, 4H, benzoxazole ring), 7.28 (2H, d, J_o=8.2 Hz, Ar-H), 7.19 (4H, d, J_o=8.1 Hz, Ar-H), 6.86 (s, 2H, N***H$_2$***), 4.96 (2H, s, H-4), 3.02 (s, 3H, 4-C***H$_3$***), 1.88 (s, 3H, 3-C***H$_3$***); ESI-MS: m/z 381 (M+Na, 41%), 359 (M+1, 13%); Anal. Calcd. for $C_{21}H_{18}N_4O_2$: C-70.38, H-5.06, N-15.63; Found: C- 70.33; H-5.01; N-15.59%.

RESULTS AND DISCUSSIONS

Chemistry

The title compounds **2(a-h)** has been obtained in good yields from the reaction of pyranopyrazoles (Sohal, 2013), **1(a-h)** with o-aminophenol and carbon disulphide according to

Scheme-1. The pyranopyrazoles were prepared according to the method as described in the literature (Sohal, 2013). The structures of newly prepared heterocycles **2(a-h)** have been fully characterized by using their various spectroscopic data such as IR, ^{1}H-NMR & ESI-MS. The elemental analysis also confirmed the purity of these compounds. IR spectrum of **2(a-h)** did not show any band in the C≡N region which described the participation of C≡N group of **1(a-h)** in the product formation.



Scheme 1.

Table-1. Minimum inhibition concentrations (µg/ml) of compounds 2(a-h)

Entry	Gram (+ve) bacteria			Gram (+ve) bacteria		
	E. coli	*K. pneumonia*	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*S. pyogenes*
2a	16	32	32	8	16	32
2b	8	16	16	32	8	32
2c	8	16	16	32	32	16
2d	8	16	8	16	8	16
2e	32	32	8	16	8	8
2f	64	8	8	32	16	32
2g	32	64	32	32	8	16
2h	8	16	8	16	8	16
Amoxicillin	4	4	4	4	4	4

Here, noticeable bands were observed at 3390-3360, 3224-3210 (N-H_2), 3142-3128 (N-H), 2952-2936, 2856-2830 (methylene C-H), 1596-1588 (C=N) & 1250-1238, 1086-1061 cm^{-1} (C-O). In ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of **2(a-h)** contained a D_2O exchangeable broad singlets present at δ 11.30-11.17 could be ascribed to pyrazole ring 1-N***H*** protons. The significant feature of these spectra were the signals of the pyran ring protons (H-4) which were clearly resonating as the one hydrogen sharp singlet at δ 5.11-4.96 whereas C_6-N$\boldsymbol{H_2}$ group generated a two hydrogens broad singlets at δ 6.95-6.84. Here, aromatic protons appeared at the suitable positions and protons of benzoxazole ring appears as a multiplet of four protons in a appropriate range. Towards the most upfield region, a singlet integrating for three protons at δ 1.94-1.80 could be ascribed to 3-C$\boldsymbol{H_3}$ group. Finally, the structure of heterocycles 2(a-h) was also corroborated from its ESI-MS spectrum.

Antimicrobial Activity

The MIC of the prepared compounds **2(a-h)** have been determined by using serial tube dilution method against the seven bacterial strains *Klebsellia pneumonia* (MTCC 3384), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 443), *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441) and *Streptococcus pyogenes* (MTCC 442). Serial tube dilution method was used to determine the minimum inhibitory concentrations of these products. The overall outcomes of these examinations were compared with the standard drug Amoxicillin. Dimethyl sulfoxide was used to prepare the concentration of 128, 64, 32, 16, 8, 4, 2 and 1 µg/ml. The bacterial strains were grown at 37°C for 24 hrs in nutrient broth. The presence of the used microbes in the analyzed compounds was evaluated by the appearance of turbidity after the above said time period. The results of minimum inhibitory concentration (MIC-µg/ml) determinations are presented in **Table-1**.

Table-1 indicates that **2a** showed good activity against the S*taphylococcus aureus* while compound **2b** displayed significant MIC against *Escherichia coli* and *Bacillus subtilis*. The product **2c** displayed noticeable antibacterial behavior against *Escherichia coli* at the MIC of 8 µg/ml. Compound 2d and **2e** provided good potency (MIC-8µg/ml) against *Escherichia coli*, *Pseudomonas aeruginosa, Bacillus subtilis* And *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Streptococcus pyogenes* respectively. Interestingly, **2f** possessed MIC of 8 µg/ml against *Klebsellia pneumonia* and *Pseudomonas aeruginosa*. Activity against *Bacillus subtilis* was provided by compound **2g** while **2h** was found to inhibit the growth of bacterial strains *Escherichia coli, Pseudomonas aeruginosa* and *Bacillus subtilis*.

Conclusion

It may be concluded that this study describes the general and highly efficient for the preparations of new pyranopyrazoles based benzoxazole derivatives. The significant advantages associated with this protocol are the good yields of products, easy work-up conditions and purification of compounds by crystallization method. The promising antimicrobial potencies of these heterocycles **2(a-h)** as compared to their starting analogues **1(a-h)** further justified the purpose of this study. It is worthwhile to mention here that compounds **2d**, **2e** & **2h** were found to exhibit noticeable antimicrobial activity as compared to other heterocycles.

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