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SYNTHESIS AND BIOLOGICAL SCREENING OF SOME HETEROCYCLES DERIVED FROM PIPERONAL

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ABSTRACT

Novel pyrazolines and benzothiazepines derivatives containing piperonal nucleus were synthesized and screened for *in vitro* anti-bacterial as well as anti-fungal activity. The synthesized compounds were characterized by IR, ^{1}H NMR and MS study. These compounds shows good to excellent bioactivities as compare with reference organism.

Key words: Pyrazoline, Benzothiazepine, Chalcone, Anti-microbial activity.

INTRODUCTION

Piperonal is familiar as heliotropin and is an organic compound that is commonly exhibited fragrances and flavours. It has a flowery odour and being similar to that of vanillin and cherry. It is used as flavouring and in perfumes[1]. The literature survey revealed that piperonal derivatives show anticonvulsant activity[2]. Due to promising bioactivities associated with the piperonal derivatives, various researchers are interested in their synthesis and structural elucidation[3]. Recently piperonal has been used for various synthetic conversation[4].

N-and/S- containing heterocycle, such as pyrazoline as well as thiazepine and its derivatives show broad spectrum of pharmacologicalactivity[5]. Thiazepinef used to a benzene ring is known as benzothiazepine, and it is connected with antifungal[6], antimicrobial[7] and anti-breast cancer activity[8].

Considerable courtesy has been attentive on pyrazoline derivatives, due to their stimulating bioactivities. They have been found to possess anti-oxidant, anti-cancer, anti-HIV, anti-malarial, anti-fungal, anti-bacterial, anti-amoebic, and anti-mycobacterial activities[9,10].

Prompted by the importance of pyrazolines and benzothiazepinesquoted in literature, synthesis and biological evaluation has been planned in present work.

EXPERIMENTAL

All the recorded melting points (^{o}C) were determined in the m.p. apparatus (Model: KI-11 [MP-D]), Make: Kumar Sales Corporation, Mumbai, India). IR spectra were recorded on a Perkin-Elmer FTIR

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spectrophotometer on a KBr disc. ^{1}H NMR spectra were recorded on a Bruker ARX spectrometer with peak values shown in δ ppm using $SiMe_4$ as the internal standard when measured in $CDCl_3$ or DMSO-d_6. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), m (multiplet), and q (quartet). Mass spectra were obtained by the Finnigan mass spectrometer. Substituted phenols and required chemicals for preparation of precursors were bought from a commercial chemical company. TLC was performed on pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany)

General procedure for the preparation of substituted 3-(benzo[d][1,3]dioxol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones (3a–e)

A 100 mL of conical flask was charged with an equivalent quantity of piperonal **1** (0.01 mol) and with variously substituted *o*-hydroxyacetophenones **2a–e** (0.01 mol) in EtOH as a solvent. A solution of 40% KOH (5 mL) solution was added and the resulting mixture allowed remaining for 24 hours at room temperature. The development of the reaction was checked by TLC. After completion, content was poured into crushed ice and acidify with conc. HCl. Solid thus obtained was separated by filtration & recrystallized from proper solvent to get chalcones **3a-e**.

The spectral data for the 3-(benzo[d][1,3]dioxol-5-yl)-1-(5-chloro-2-hydroxy-4-methylphenyl) prop-2-en-1-one (3a)

FT-IR (KBr) ν_{max} (cm^{-1}): 3325, 3022, 1629, 1587, 1500, 1257, 700; ^{1}H NMR (300 MHz, $CDCl_3$): 2.33 (3H, s, CH_3), 5.90 (2H, s, -OCH_2), 6.017-6.069 (1H, d, J = 15.6 Hz), 7.363-7.414 (1H, d, J = 15.3 Hz), 6.87-7.88 (5H, m, ArH), 12.78 (1H, s, -OH); MS, ES + 1 mode (m/z): 317.0 (M + 1).

General procedure for the preparation of substituted 2-(5-(benzo[d][1,3]dioxol-5-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenols (pyrazolinesderivatives) (4a–e)

To a solution of chalcone (0.01 mol) (3a–e) in 10 mL of ethanol, 1.5 mL (0.048 mol) of hydrazine hydrate (99%) and 2–3 drops of glacial acetic acid were added drop wise. The reaction mixture was heated under reflux for 6 h and the progress of the reaction checked by TLC. After completion of the reaction, the reaction mixture was cooled and poured into crushed ice. The solid pyrazolines (4a-e) were filtered and recrystallized from EtOH.

The spectral data for the 2-(5-(benzo[d][1,3]dioxol-5-yl)-4,5-dihydro-1H-pyrazol-3-yl)-4-chloro-5-methylphenol(4a)

FT-IR (KBr) max (cm^{-1}): 3380, 3301, 3066, 3016, 1583, 1473, 1247, 702; ^{1}H NMR (300 MHz, $CDCl_3$): 2.35 (3H, s, CH_3), 3.027-3.111 (1H, dd, J = 8.7, 7.8 Hz, pyrazoline H), 3.442-3.533 (1H, dd, J = 10.8, 5.7 Hz, pyrazoline H), 4.797-4.861 (1H, dd, J = 10.8, 8.7 Hz, pyrazoline H), 5.97 (2H, s, -OCH_2), 7.11 (1H, s, NH), 6.76-7.28 (5H, m, ArH), 10.85 (1H, s, -OH); MS, ES + 1 mode (m/z): 331 (M + 1).

General procedure for the preparation of 2-2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo[b][1,4] thiazepin-4-yl)phenols (benzothiazepine derivatives) (5a–e)

To a solution of chalcone (0.01 mol) (5**a-e**) in 10 mL of ethanol, 0.01 mol of *o*-amino thiophenol and 2-3 drops of glacial acetic acid were added. The reaction mixture was refluxed by heating for 6 hours, and the progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was cooled and transferred into crushed ice. The solid product was filtered and recrystallized from EtOH to enable benzodiazepine derivatives **5a-e**.

The spectral data for the 2-(-2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo[b] [1,4]thiazepin-4-yl)-4-chloro-5-methylphenol (5a)

FT-IR (KBr) ν_{max} (cm^{-1}): 3344, 3031, 2970, 1589, 1487, 1278,686; ^1H NMR (300 MHz, $CDCL_3$): 2.34 (3H, s, CH_3), 2.854-2.939 (1H, t, J = 12.9 Hz thiazepine ring), 3.381-3.515 (1H, dd, J = 12.5, 4.5 Hz, thiazepine ring), 5.253-5.308 (1H, dd, J = 7.2, 4.5 Hz thiazepine ring), 5.99 (2H, s, -OCH_2), 6.84–7.79 (9H, m, ArH), 14.29 (1H, s, -OH exchangeable); MS, ES+1 mode (m/z): 424 (M + 1).

Pharmacological Assay

Antimicrobial activity

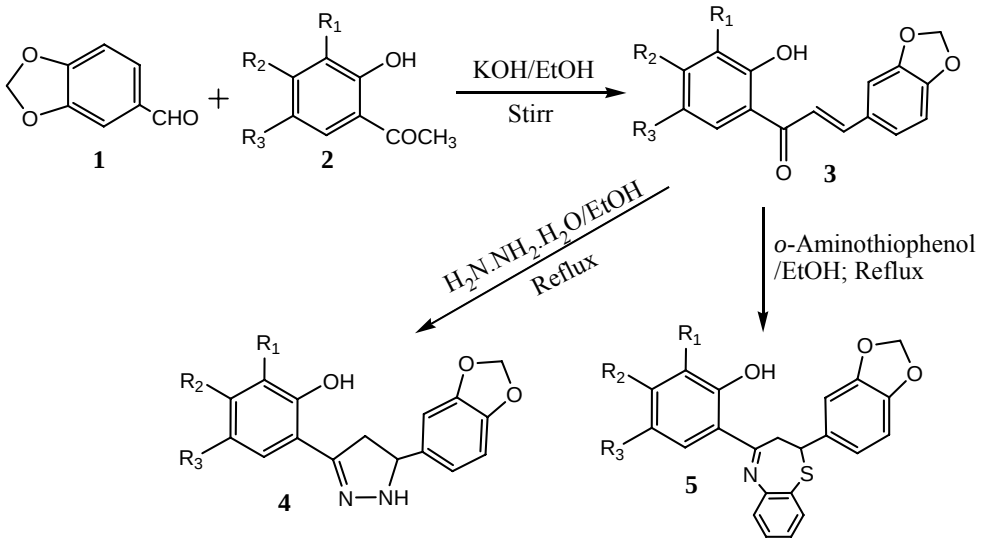
Antimicrobial activities were determined by agar diffusion assay disc method against *S. Aureus, Pseudomonas aeruginosa* bacteria and *Aspergillusniger, Candida albicans* fungi. The antibiotic Nystatin (100U/disc) and Chlorampenicol (10 mcg/disc) was used as a control for antibacterial and antifungal activity respectively. The samples (100 µg/mL) were dissolved in dimethyl sulphoxide (DMSO) and used for the antimicrobial activities. The bacterial cultures of known inoculums size (1 x 10^8 bacteria/mL) of the test microorganism were spread on Muller Hinton agar plates. While the fungal cultures of known inoculums size (1 x 10^6 bacteria/mL) of the test microorganism were spread on Potato dextrose ager plates.

The Watman filter paper discs of 6 mm were placed on the plate and the sample of appropriate concentrarion was added to the filter disc. The plates were further in cubed for 19-22 hrs at 40°C.

RESULTS AND DISCUSSION

Synthesis of compound 4 and 5

The synthetic route used to synthesize the target compound **4** and **5** is outlined in **Scheme 1**. Variously substituted *o*-Hydroxyacetophenones has been prepared by Fries rearranged from phenols.



Scheme 1: Synthesis of Pyrazolines 4 and benzothiazepines 5

Chalcones **3a–e** was prepared by the Claisen–Schmidt condensation reaction of piperonal **1** and variously substituted *o*-hydroxyacetophenones **2** in the basicmedium. The target compounds **4** and **5** were synthesized by Michael addition of hydrazine hydrate and *o*-amino thiophenol to chalcones **3** respectively in acetic acid/ethanol.

In general, spectral data is in good agreement with structure and with the theoretical values. The ^{1}H NMR of chalcone shows two doublets of trans olefins with J = 15.6 Hz.

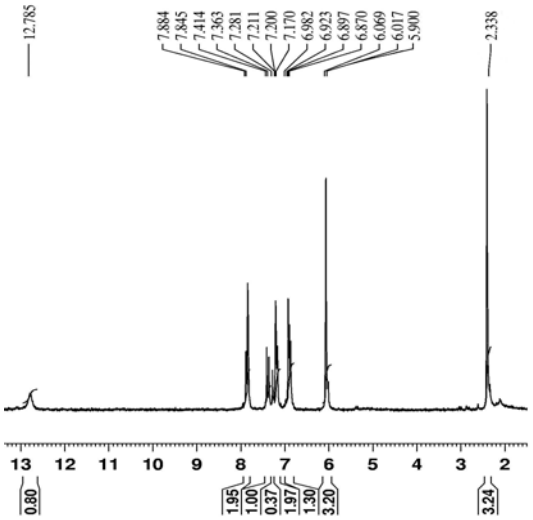


Fig. 1: ^{1}H NMR of Chalcone 3a

The three protons of pyrazoline nuclei in the pyrazoline derivatives **4a-e** followed the AMX pattern and shows three doublet of doublet (dd). It is no doubt for conformation of pyrazoline nucleus in the present investigation.

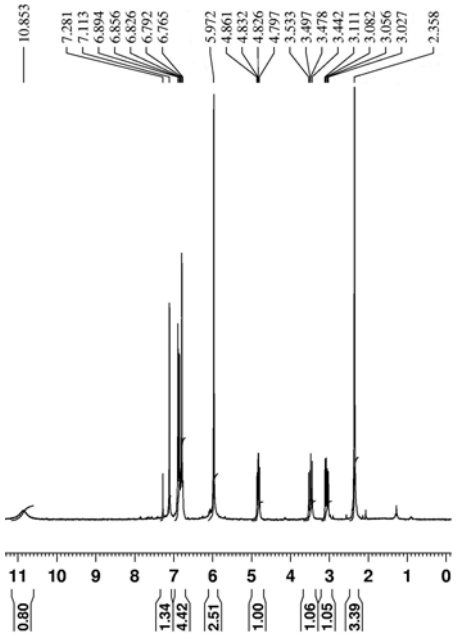


Fig. 2: ^{1}H NMR of Pyrazoline 4a

The three thiazepine protons of known benzothiazepines **5a–e** showed similar patterns of signals in ^{1}H NMR. They displayed doublet of doublet (dd) for two protons and triplet (t) for one proton. One signal is observed as a triplet instead of a doublet of a doublet (dd) because two *J*-values accidentally are the same and two inner lines of the quartet occur at the same point, appearing as a single line of double the intensity[11].

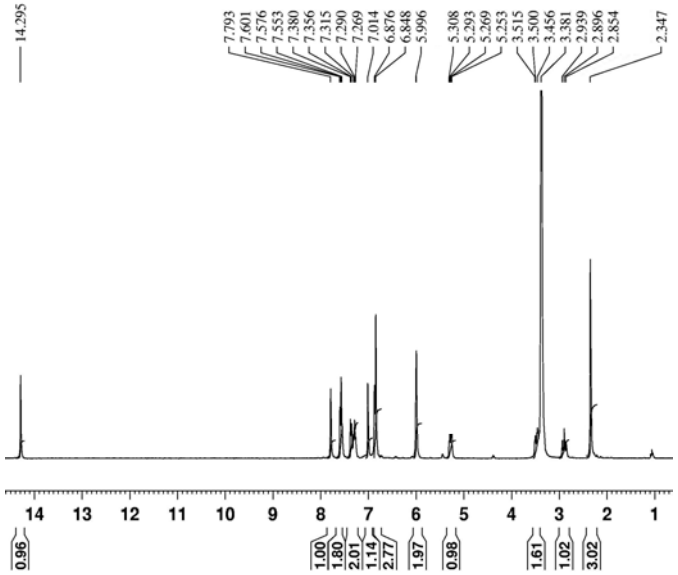


Fig. 3: ^{1}H NMR of benzothiazepine 4a

The structure of the synthesized compounds was confirmed by above spectral studies. The characterization data are summarized in Table 1.

Table 1: Data of compound 3a-e, 4a-e, 5a-e

Entry	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
3a	H	CH_3	Cl	200-202	71
3b	H	H	CH_3	112-114	72
3c	Cl	H	Cl	180-182	78
3d	H	H	Cl	146	78
3e	H	H	H	115	76
4a	H	CH_3	Cl	120	78
4b	H	H	CH_3	110	78
4c	Cl	H	Cl	122-124	72
4d	H	H	Cl	76	77
4e	H	H	H	98	76
5a	H	CH_3	Cl	172	80
5b	H	H	CH_3	184-186	72
5c	Cl	H	Cl	90	66
5d	H	H	Cl	162-164	68
5e	H	H	H	95	69

Biological evaluation

Obtained results from the antimicrobial evaluation are summarized in Table 2.

Table 2: Antimicrobial activity of synthesized compounds 4 and 5

Entry	Zone of inhibition			
	S. aureus	***Pseudomonas aeruginosa***	***Aspergillusniger***	***Candida albicans***
4a	16	19	17	13
4b	17	20	18	15
4c	22	22	23	18
4d	18	--	20	17
4e	--	12	13	15
5a	20	21	18.2	15
5b	14	16	13	13.3
5c	27	26	18	18
5d	25	23	16	17
5e	10	11	09	11
Nystatin	NA	NA	20.14	22.84
Chlorampenicol	30.8	25.01	NA	NA

Abbreviations used: NA = Not applicable, - -= No zone of inhibition*

Diameter in mm calculated by digital vernier Caliper

The study of antimicrobial screening data shown that all the tested compounds **4** and **5** showed good to excellent antibacterial and antifungal activities against *S. Aureus, Pseudomonas aeruginosa and Aspergillusniger, Candida albicans*respectively. The **4a-e** is active against all species except **4d** and **4e** against *Pseudomonas aeruginosa* and *S. Aureus*, respectively. Among pyrazolines **4c** are the most active compounds and are passive for all bacterial as well as fungal species. Amongpyrazolines **4c** showed excellent bioactivities comparable with standard drug Chlorampenicol.

Amongbenzothiazepines **(5a-5e) 5c** and **5d** exhibited good activity as compare with reference compound Chlorampenicol and Nystatin. The most active compounds **4c** and **5c** are passive for both bacterial and fungal strains.

CONCLUSION

All the synthesized compounds are obtained in good yield and theoretical spectral values are matched with current spectral data. Among all tested compounds, chloro-substituted pyrazolines and benzothiazepine derivative **4c** and **5c** showed the highest anti-antimicrobial activity that was comparable to reference drug. However, none of the newly synthesized compounds were foundto be superior to the reference drug.

SAR study: From the bioactivity results, we concluded that the newly synthesized benzothiazepine derivatives containing chlorine as a substitute areable to show the highest anti-microbial activity, whereas those compounds containing hydrogen as a substitute show the lowest anti-microbial activity.

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REFERENCES

1. K. G. Fahlbusch, F. J. Hammerschmidt, J. Panten, W. Pickenhagen, D. Schatkowski, K. Bauer, D. Garbe and H. Surburg, Flavors and Fragrances, in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim (2003) p. 141.
2. J. Ankunuru, K. Edula, V. Pashan, V. Katala and S. Reddy, Int. J. Pharm. Sci. Nanotech., **2(1)**, 435 (2009).
3. A. Echevarriaa, M. G. Nascimentob, V. Gerônimob, J. Millerc and A. Giesbrechtd, J. Braz. Chem. Soc., **10(1)**, 60 (1999).
4. S. A. Shiba, A. K. El-Ziaty, N. K. El-Aasar and H. A. AJ-Saman, J. Chem Res., **(9)**, 500 (2008)
5. M. Struga, J. Kossakowski, A. E. Koziol, E. Kedzierska, S. Fidecka, P. L. Colla, C. Ibba, G. Collu, G. Sanna, B. Secc and R. Loddod, Eur. J. Med. Chem., **44**, 4960 (2009).
6. A. J. Khan, M. A. Baseer, J. M. Dhole, S. N. Shah, Int. J. Pharma. Sci. Res., **2(10)**, 2619 (2011).
7. N. Garg, T. Chandra, A. B. Jain and A. Kumar, Eur. J. Med. Chem., **45**, 1529 (2010).
8. K. L. Ameta, N. S. Rathore and B. Kumar, J. Serb. Chem. Soc., **77 (6)**, 725 (2012).
9. S. Kumar, S. Bawa, S. Drabu, R. Kumar and H. Gupta, Recent Pat. Anti-infect Drug Discov., **4**, 154 (2009).
10. T. Taj, R. R. Kamble, T. M. Gireesh, R. K.Hunnur abd S. B. Margankop, Eur. J. Med.Chem., **46**, 4366 (2011).
11. P. S. Kalsi, An Introduction to More Complex ^{1}H NMR Spectrs and Spin-spin Splitting, In The Spectroscopy of Organic Compounds, 6th Ed., New Age International Publishers: New Delhi (2010) p. 282.