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Microwave-assisted synthesis of novel 4*H*-chromene derivatives bearing phenoxypyrazole and their antimicrobial activity assessment

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Abstract: A new series of 4*H*-chromene derivatives **4a**–**p** bearing the 5-phenoxypyrazole nucleus were synthesized under microwave irradiation by the reaction of 5-phenoxypyrazole-4-carbaldehydes **1a**–**h**, malononitrile **2** and compounds 1,3-cyclohexanedione and dimedone (**3a** and **3b**, respectively) in presence of NaOH as a basic catalyst. All the compounds were screened against three Gram-positive bacteria (*Streptococcus pneumoniae*, *Clostridium tetani* and *Bacillus subtilis*), three Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae* and *Escherichia coli*) and two fungi (*Aspergillus fumigatus* and *Candida albicans*) using the broth microdilution minimum inhibitory concentration (MIC) method. The antimicrobial screening showed that the majority of the compounds were active against *C. tetani* and *B subtilis* as well as against *C. albicans* when compared with standard drugs.

Keywords: phenoxypyrazole; 4*H*-chromene; multi-component reaction; microwave irradiation; antimicrobial activity.

INTRODUCTION

The steadily increasing microbial resistance to existing first line drugs is a serious problem in antimicrobial cure and necessitates continuing research into new classes of antimicrobials.[1] Moreover, the progression of drug-resistant strains has contributed to the inefficiency of the straight antimicrobial therapy. This issue has provoked enormous interest in antimicrobial research and it is strongly believed that there is an urgent call for the development of new drugs with divergent and unique structures and probably with an unusual mechanism of action differing from that of existing first line drugs.

The chromene ring system is considered one of the most imperative heterocycles in nature as it has the distinction of being the parent ring in countless

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derivatives of biological relevance. The current interest in 4*H*- and 2*H*-chromene derivatives arises from their potential application as antimicrobial,[2] anti-HIV,[3] antitubercular,[4] antioxidant,[5] anticancer,[6] antitumor,[7] cytotoxic agents,[8] antidyslipidemic agent,[9] antileishmanial,[10] anti-inflammatory,[11] anti-Helicobacter pylori agent[12] and TNF-α inhibitor.[13] On the other hand, pyrazole derivatives are also well-known for their biological properties, including antimicrobial,[14–16] anti-inflammatory (COX-2 inhibitor and ulcerogenic activity),[15] antitubercular,[16] antitumor,[17] anti-angiogenesis,[18] antiparasitic,[19] antiviral,[20] analgesic and anxiolytic activity.[21]

Moreover, the most suitable protocol for the synthesis of functionalized organic compounds could be a multicomponent reaction (MCR) because the synthesis could be performed without the isolation of the intermediates, without discharging any functional groups and within short reaction time.[22]. In addition, the conventional procedures are not found to be satisfactory with regard to operational simplicity, effectiveness and yield. An alternative synthetic approach is microwave irradiation.[23] In recent years, microwave irradiation has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity.

Thus, in view of biological significance of 4*H*-chromene, a modification on the 4-position on pyrane by 5-phenoxypyrazole was undertaken to check whether it may bring significant changes in the bioactivities of 4*H*-chromene derivatives. As a part of current studies in developing new antimicrobial agents *via* combination of two therapeutically active moieties,[24] the synthesis of 4*H*-chromene derivatives **4a**–**p** by MCR are reported herein.

All the compounds were characterized using elemental analysis, FT-IR, ^{1}H--NMR and ^{13}C-NMR spectroscopy, and the molecular weights of some selected compounds were confirmed by mass spectroscopy. All compounds were screened for *in vitro* antimicrobial activity against eight human pathogens, *i.e.*, three Gram-positive bacteria (*Streptococcus pneumoniae*, *Clostridium tetani* and *Bacillus subtilis*), three Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholera* and *Escherichia coli*) and two fungal pathogens (*Aspergillus fumigates* and *Candida albicans*) using the broth microdilution minimum inhibitory concentration (MIC) method.[25]

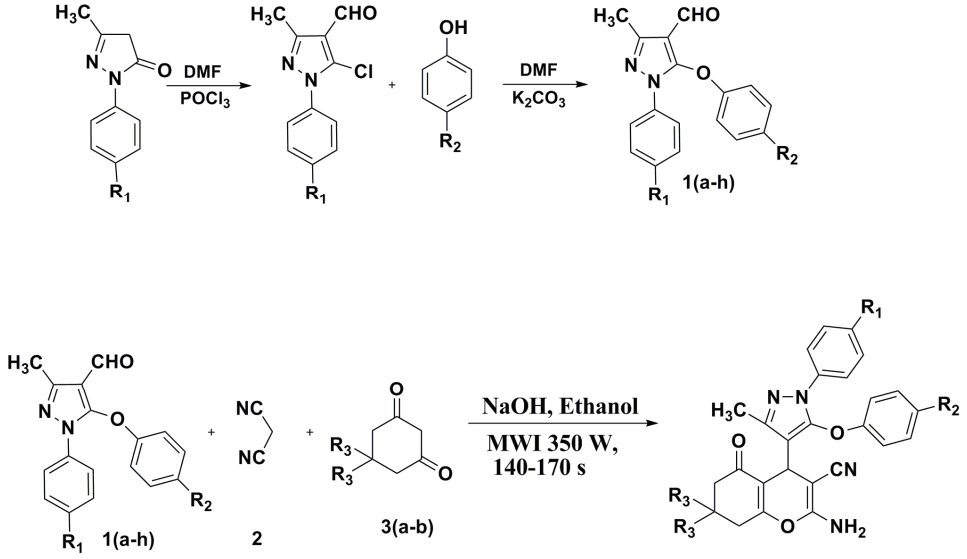
RESULTS AND DISCUSSION

Chemistry

The key intermediates, 3-methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehydes **1a**–**h** were prepared by refluxing 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde and various phenols in the presence of anhydrous potassium carbonate in dry dimethylformamide (DMF) for 3.5 h.[24a] The required 1-aryl-5-

-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde was prepared by the Vilsmeier–Haack reaction according to a literature procedure.[26]

In the present study, 4*H*-chromene derivatives **4a**–**p** were synthesized in moderate to good yield, *i.e*., 68–90 %, by reaction of **1a**–**h**, malononitrile **2** and compounds **3a**–**b** under microwave irradiation in the presence of NaOH as a basic catalyst (Scheme 1).



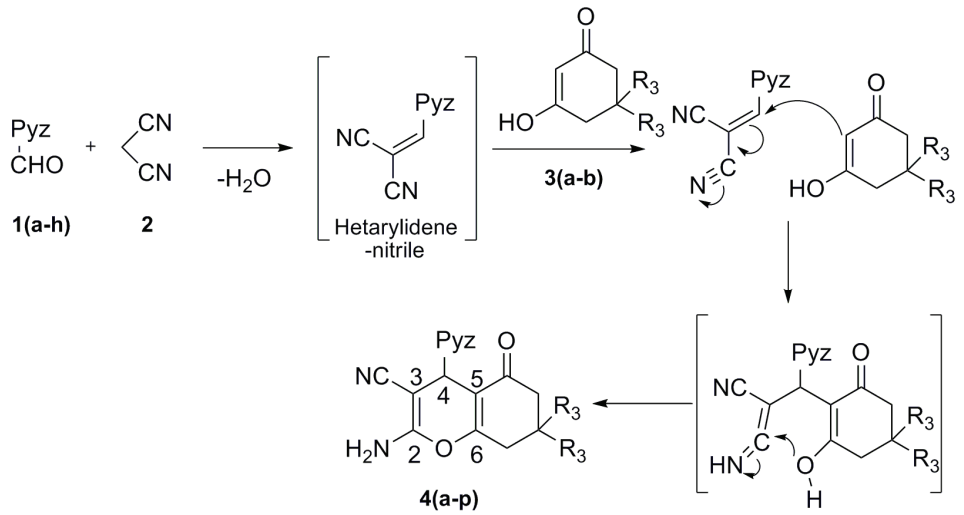
Comp.	R_1	R_2	R_3	Yield[a], %	Comp.	R_1	R_2	R_3	Yield[a], %
4a	H	H	H	78	**4i**	H	H	CH_3	90
4b	H	CH_3	H	90	**4j**	H	CH_3	CH_3	75
4c	H	OCH_3	H	84	**4k**	H	OCH_3	CH_3	87
4d	H	Cl	H	69	**4l**	H	Cl	CH_3	65
4e	CH_3	H	H	80	**4m**	CH_3	H	CH_3	88
4f	CH_3	CH_3	H	84	**4n**	CH_3	CH_3	CH_3	90
4g	CH_3	OCH_3	H	72	**4o**	CH_3	OCH_3	CH_3	92
4h	CH_3	Cl	H	64	**4p**	CH_3	Cl	CH_3	73

[a]All yields are isolated yields

Scheme 1. Synthetic pathway for the synthesis of 4*H*-chromene derivatives bearing the phenoxypyrazole core **4a**–**p**.

In convenient electrochemical processes, organic basic catalysts, such as piperidine and triethylamine, were used in the synthesis of many 4*H*-chromene derivatives[27] but in the present study, NaOH was used as the basic catalyst to avoid the employment of hazardous organic bases. Furthermore, during attempts to synthesize the title compounds by the conventional method, some shortcomings in this method were observed, such as longer reaction time, drastic reac-

tion conditions and poor yield. Consequently, to overcome these drawbacks, the microwave irradiation method was used in the present study for the synthesis of title compounds. In accordance with the mechanism suggested in literature,[28] the first step of this process may involve Knoevenagel condensation of the aldehyde and malononitrile to gives heterylidenenitrile derivatives, which was followed by Michael addition of **3a**–**b** to the heterylidenenitrile to afford the title compounds **4a**–**p** (Scheme 2).



Pyz-CHO = 3-Methyl-5-aryloxy-1-aryl-1*H*-pyrazole-4-carbaldehyde
R_3 = H, CH_3

Scheme 2. Plausible mechanistic pathway of the synthesis of 4*H*-chromene derivatives **4a**–**p**.

The structures of all the newly synthesized compounds were confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy, and elemental analysis. The physical, analytical and spectral data of all the synthesized compounds **4a**–**p** are given in the Supplementary material to this paper. The IR spectrum of title compounds **4a**–**p** revealed the presence of amino, cyano, carbonyl and ether groups through the appearance of absorption bands at around 3370–3430, 3170–3350, 2190–2220, 1630–1710 and 1190–1230 cm^{-1}, respectively. Their ^{1}H-NMR spectra indicated the presence of a singlet in the range δ 4.12–4.38 ppm of the CH proton and the disappearance of a singlet at δ 9.57–9.63 ppm of –CHO, which clearly confirmed the cyclization of the Knoevenagel intermediates. Moreover, multiplets in the range δ 6.59–7.55 ppm appeared for aromatic protons. In the ^{13}C-NMR spectral data of the title compounds **4a**–**p**, most characteristic signal around δ 24.50–25.25 ppm indicate the formation of the pyrane ring. The signal at around δ 56.20–60.64 ppm is assigned to carbon attached to carbonitrile, while signals around δ 110.20–164.50 and 196.10–196.35 ppm are attributed to all the

aromatic and carbonyl carbons, respectively, of compounds **4a**–**p**. The obtained elemental analysis values are in good agreement with theoretical data. Furthermore, the molecular weight of selected compounds, *i.e.*, **4c**, **4i** and **4o**, were confirmed by mass spectral studies. The mass spectra of these compounds showed a molecular ion peak $[M+1]^+$ corresponding to the exact theoretical mass.

Biological evaluation

All the compounds were screened for their antibacterial and antifungal activity and the results are presented in Table I, expressed in the form of *MIC* in μg mL^{-1}.

TABLE I. Antimicrobial activity of compounds **4a**–**p** (minimum inhibitory concentration (*MIC*), μg mL^{-1}); Bs.: *B. subtilis*; Ct.: *C. tetani*; Sp.: *S. pneumoniae*; Ec.: *E. coli*; St.: *S. typhi*; Vc.: *V. cholerae*; Af.: *A. fumigatus*; Ca.: *C. albicans*; MTCC: microbial type culture collection; A: ampicillin; B: ciprofloxacin; C: norfloxacin; D: chloramphenicol; E: nystatin; F: griseofulvin. "–" represents "not tested"

Compound	Gram-positive bacteria			Gram-negative bacteria			Fungal species	
	Bs. MTCC 441	Ct. MTCC 449	Sp. MTCC 1936	Ec. MTCC 443	St. MTCC 98	Vc. MTCC 3906	Af. MTCC 3008	Ca. MTCC 227
4a	500	500	500	250	500	500	>1000	>1000
4b	250	500	250	500	500	100	500	500
4c	500	500	500	200	500	500	250	250
4d	1000	100	500	250	500	200	250	100
4e	250	200	250	500	250	200	500	250
4f	500	200	500	250	250	200	500	500
4g	500	250	500	250	500	100	500	200
4h	500	200	500	100	500	250	250	250
4i	250	500	250	100	100	250	1000	500
4j	500	100	500	250	62.5	250	1000	1000
4k	500	250	500	500	500	200	500	250
4l	250	200	250	250	250	200	500	250
4m	500	500	50	250	500	500	1000	500
4n	62.5	100	250	100	62.5	200	>1000	>1000
4o	500	100	500	200	500	200	500	500
4p	250	250	500	100	62.5	250	250	250
A	250	250	100	100	100	100	–	–
B	50	100	50	25	25	25	–	–
C	100	50	10	10	10	10	–	–
D	50	50	50	50	50	50	–	–
E	–	–	–	–	–	–	100	100
F	–	–	–	–	–	–	100	500

An examination of the data prescribed in Table I revealed that many of the compounds were more potent or equipotent to the standard drugs against the Gram-positive bacteria *C. tetani* and a few against *S. pneumoniae* and *B. subtilis*.

Against the Gram-positive bacteria *B. subtilis*, compound **4n** (*MIC* = 62.5 μg mL^{-1}) was found to be more potent, whereas **4b**, **4e**, **4i**, **4l**, and **4p** (*MIC* = 250 μg mL^{-1}) shows comparable activity to ampicillin (*MIC* = 250 μg mL^{-1}). Moreover, compound **4n** (*MIC* = 62.5 μg mL^{-1}) was found to more active as compared to norfloxacin (*MIC* = 100 μg mL^{-1}). Against *C. tetani*, compounds **4d**, **4j**, **4n** and **4o** (*MIC* = 100 μg/mL), and **4e**, **4f**, **4h** and **4l** (*MIC* = 200 μg mL^{-1}) were found to be more potent, whereas **4g**, **4k** and **4p** (*MIC* = 250 μg mL^{-1}) showed comparable activity to ampicillin (*MIC* = 250 μg mL^{-1}), while compounds **4d**, **4j**, **4n** and **4o** (*MIC* = 100 μg mL^{-1}) were equally potent as compared to ciprofloxacin (*MIC* = 100 μg mL^{-1}). Against *S. pneumoniae*, compound **4m** (*MIC* = 50 μg mL^{-1}) showed comparable activity to chlormphenicol and ciprofloxacin (*MIC* = 50 μg mL^{-1}).

Towards the Gram-negative strain *E. coli*, compounds **4h**, **4i**, **4n** and **4p** (*MIC* = 100 μg mL^{-1}) showed comparable activity to ampicillin (*MIC* = 100 μg mL^{-1}). Compounds **4j**, **4n** and **4p** (*MIC* = 62.5 μg mL^{-1}) were more potent, whereas **4i** (*MIC* = 100 μg mL^{-1}) showed comparable activity to ampicillin (*MIC* = 100 μg mL^{-1}) towards *S. typhi.* Also the compounds **4b** and **4g** (MIC = 100 μg/mL) show comparable activity, to ampicillin (MIC=100 μg/mL) towards *V. cholerae.*

Comparison of the data for compounds **4a**–**d** with those for **4e**–**h** showed that on replacement of H with CH_3, the poorly active compounds **4a**, **4b** and **4c** (*MIC* = 500 μg mL^{-1} against *C. tetani*) were converted to the highly potent **4e**, **4f** and **4g**, respectively, while the potency of compound **4d**, where R_2 = Cl, against *C. tetani* decreased on introduction of CH_3 at R_1. Against *B. subtilis*, comparing compound **4f** with **4n**, it was observed that the poorly active compound **4f** (*MIC* = 500 μg mL^{-1}) led to the excellent activity of **4n** (*MIC* = 62.5 μg mL^{-1}), compared to the activity of ampicillin and norfloxacin. Similarly, against the Gram-negative bacteria *S. typhi*, it was observed by comparing compound **4b** with **4j** and **4f** with **4n**, that poorly active compounds were converted to highly active ones (*MIC* = 62.5 μg mL^{-1}) as compared with ampicillin (MIC = 100 μg mL^{-1}), *i.e*., the compound having a *gem* dimethyl group on the benzopyran ring showed increased antibacterial activity.

Against fungal pathogen *C. albicans*, compounds **4d** (*MIC* = 100 μg mL^{-1}), **4g** (*MIC* = 200 μg mL^{-1}) **4c**, **4e**, **4h**, **4k**, **4l** and **4p** (*MIC* = 250 μg mL^{-1}) showed good to excellent activity, whereas **4b**, **4f**, **4i**, **4m** and **4o** (*MIC* = 500 μg mL^{-1}) were equipotent to griseofulvin (*MIC* = 500 μg mL^{-1}). Compound **4d** (*MIC* =100 μg mL^{-1}) was found equipotent to nystatin towards *C. albicans.*

The remaining compounds showed moderate to good activity in the inhibition of the growth of bacterial pathogens and were all less effective than the standard drugs. From the antimicrobial study of the title derivatives, it is inte-

resting to note that a minor alteration in the molecular structure of the investigated compounds may have a pronounced effect on antimicrobial activity.

EXPERIMENTAL

Materials, instruments and methods

The required chemicals were obtained from S. D. Fine Chem Ltd., Vadodara, Gujarat, India. 1,3-Cyclohexanedione and dimedone were obtained from Sigma-Aldrich. The solvents were purified and dried before use. The microwave assisted reactions were conducted in a "RAGA modified electromagnetic microwave system", whereby the microwaves were generated by a magnetron at a frequency of 2450 MHz having adjustable output power levels, *i.e.*, 10 levels from 140 to 700 W and with an individual sensor for temperature control (fiber optic was used as an individual sensor for temperature control). A reflux condenser was attached to the reaction flask and the reactions were performed under constant stirring (thus avoiding the risk of high pressure development). All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates pre-coated with silica gel, 60 F254, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, and the purity and homogeneity of the synthesized compounds. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was realized using a Perkin-Elmer 2400 Series-II elemental analyzer (Perkin-Elmer, USA) and the results for all compounds were within ±0.4 % of the theoretical values. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. The ^{1}H-NMR and ^{13}C--NMR spectra were recorded at 400 and 100 MHz, respectively, in DMSO-d_6 on a Bruker Avance 400F spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using the solvent peak as internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer.

*Conventional synthesis of compounds **4a**–**p***

Phenoxypyrazole-4-carbaldehyde **1a**–**h** (10 mmol), malononitrile **2** (10 mmol) and 1,3--cyclohexanedione/dimedone **3a**–**b** (10 mmol) were thoroughly mixed in ethanolic NaOH (5 mmol, 10 mL) and charged into a round bottom flask. Then the reaction mixture was refluxed for 3–3.5 h. Completion of the reaction was monitored by TLC. The solid product **4a**–**p** that separated was filtered off, washed well with ethanol (10 mL), dried and crystallized from chloroform to obtain the pure solid sample **4a**–**p**.

*Microwave-induced synthesis of compounds **4a**–**p***

Phenoxypyrazole-4-carbaldehyde **1a**–**h** (10 mmol), malononitrile **2** (10 mmol) and 1,3--cyclohexanedione/dimedone **3a**–**b** (10 mmol) were thoroughly mixed in ethanolic NaOH (5 mmol, 10 mL) and irradiated in microwave oven at 350 W (50 % of the maximum output power) for 140–170 s. After completion of the reaction (checked by TLC), the solution was cooled to room temperature, the separated solid was filtered, washed well with ethanol (10 mL), dried and crystallized from chloroform to obtain the pure solid samples **4a**–**p**.

CONCLUSIONS

A series of some new 4*H*-chromene derivatives **4a**–**p** bearing the phenolxy-pyrazole nuclei were synthesized through a facile one-pot multicomponent reaction under microwave irradiation. This synthetic strategy allowed the construc-

tion of a relatively complicated nitrogen- and oxygen-containing heterocyclic system, as well as the introduction of various aromatic and heteroaromatic substituents at the 4-position of pyrane. From the studied compounds, it was noticed that the most effective antibacterial members had a methyl group on the *N*-phenyl ring of the pyrazole moiety as well as a *gem* dimethyl group on the benzopyrane ring with either Cl or methyl substituent on the O-phenyl ring of the pyrazole moiety. The antifungal activity of the compounds shows that most of the compounds were more potent against *C. albicans* than against *A. fumigatus*. It is worth mentioning that minor changes in the molecular configuration of these compounds profoundly influenced the activity. The present study throws light on the identification of this new structural class as antimicrobials, which could be of interest for further detailed preclinical investigations.

SUPPLEMENTARY MATERIAL

Analytical, physical and spectroscopic data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА ФЕНОКСИПИРАЗИНИЛ-4*H*-ХРОМЕНА ПОД УСЛОВИМА ЗРАЧЕЊА МИКРОТАЛАСИМА И ОДРЕЂИВАЊЕ ЊИХОВЕ АНТИМИКРОБНЕ АКТИВНОСТИ

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Нова серија деривата 4*H*-хромена **4a**–**p** који садрже 5-феноксипиразол синтетисани су под условима озрачивања микроталасима, реакцијом 5-феноксипиразол-4-карбалдехида **1a**–**h**, малононитрила **2** и једињења (1,3-циклохександион, димедон) **3a**–**b** у присуству NaOH или базних катализатора. Свим једињењима испитана је активност према 3 врсте грам-позитивних бактерија (*Streptococcus pneumoniae*, *Clostridium tetani* и *Bacillus subtilis*), 3 врсте грам-негативних (*Salmonella typhi*, *Vibrio cholerae* и *Escherichia coli*) и две врсте гљива (*Aspergillus fumigatus* и *Candida albicans*) користећи поступке одређивања МИК (минимална инхибиторна концентрација разблажењем). Током испитивања антимикробне активности утврђено је да су једињења активна према *C. tetani* и *B. subtilis*, као и према *C. albicans* у поређењу са вредностима стандардних лекова.

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