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Green Synthesis of Chromenes Derivatives from *Calea pinnatifida (R. Br.) Less* and Their Antimicrobial Potentiality

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Herbs are eternally recognized to be vociferous of plural bioactive phytochemicals. Since antiquated time oodles of herbs were used by universal healers and local habitants for treaty with variant diseases. Detrimental attribute of drugs governed in our body can't be overlooked, because constantly these side effects are generally fatal. The pharmacological behaviour of illness began emboldened with the use of therapeutic plants. Cognizants of kindred curative during the war factually used herbs as personification of their custom. 'Chromene derivatives from Calea Pinnatifida (R.Br.) Less' are an enlighten category of compounds, influence embedded in plants, inclusive of edible vegetables and fruits. Lots of bioactive intrinsic products have been discovered, and the presence of the chromene-based structure has been linked with the merits to intercept

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disease. Artificial replications have been symbolized over the years, some of them displaying unbeatable effects as safeguards viz. 'antifungal, anti-microbial, molluscidial, anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactic' highlights. The term green chemistry and environmentally benign synthesis have been floated to refer to procedures specificity designed to minimize the evolution of ominous that existing disposal problems. Both the 'National Science Foundation' and the 'Environmental Protection Agency (EPA)' have sanctioned handsome percentage of funds to motivate people in this campaign.

Keywords: Green chemistry; chromene; Asteraceae; antibacterial and antifungal activity.

1. INTRODUCTION

In 1992, the World Health Organization (WHO) Divisional headquarter for the Western Pacific invited a delegation of intellectuals to build up purview and imprecise values to supervise investigations on consciousness herbal enforcements [1]. Plausible herbal materials imminent temperament scientifically, even though the incompetency reciprocating from their conventional use amidst should not be unobserved. Exempted adequate conception projected by general technical utterance to questionnaire of protection and efficiency about ordinarily herbal drugs now prescribed, the balanced use and further expansion of herbal drugs repository by more pertinent and systematic studies of these goods, and thus the development of criterion for such escalation.

Bharat is one of the 12 mega illusion centers having over 45,000 plant varieties. Its divergent is matchless due to the ushering of several dissimilar agro climatic zones, vegetative zones and biotic provinces [2]. The continent has thousands of flowering plants, 23 thousand fungi, 2 thousand 5 hundred algae, 1 thousand 6 hundred lichens, 1 thousand 8 hundred bryophytes and Thirty million micro-organisms. Corresponding to three forth of its geology restricted periphery in the sea harboring a bulky diversification of vegetation and fauna, many of them with beneficial properties (National Research Council, 1981) [3]. About 1 thousand 5 hundred plants with remedial comprehensible in antique narrative and approximately 800 plants have been used in established medicine. The revenue of herbal drugs in India as over-the-counter goods, moral and traditional conceptualisation and home remedies of various medicinal systems are about $1 billion with a not enough business of about $80 million. 80% of the exports to urbanized counterparts are of rudimentary drugs and not final formulations leading to merely returns denominate GDP. Thus, the consignment of herbal drugs from India is paralyzed even with the fact that the country has a rich established contemplation and birthright of herbal inspiration [3].

Herbal Medicine is the metaphysics blessings of healthcare reciprocated worthwhile. Herbs had been used by all worshipped throughout centenarians. It was a subjective part of the development of modern civilization, primitive man benediction and praiseworthy the transparent differentiation of plants available. The earth is witnessing an unrivalled growth in apply of herbal arena. Numerological emphatically herbal medical panorama has been explained for the diagnosis, prevention and treatment of various complexicity [4]. Many such prayers were evidently proved assets of the scientific intuition noumenon concurrence captivation.

Based on the attribute of the intermingled, somehow 02 mechanisms enlightened on simultaneous hypothesis (i.e., pharmacodynamics and pharmacokinetic). Herbal operators progressively expressible in health-care in both advanced and emergent countries. Existed complex chemical mixtures prepared from plants and are controversy in their authenticity because they are seldom surrendered when injected via mouth.

In recent times, however, the effluent rectification is often viewed as causing more harm than good. There can be no doubt that in years past, and even at present, chemistry has been comeuppance, such as the release of pollutants and toxic substances and the production of non biodegradable materials, declaring in sobered up the environment and living things, including scriptures [4,5]. The biggest arduous for the chemical Multinational Corporation (MNC) in the 21st century is to continue to provide the benefits it has provided but without deterioration environmental side effects. Fortunately, the practice of chemical science is moving steadily in the direction of ecological obedient and resources sustainability.

'Green chemistry in Day-to-Day Life':

A few examples of the chemicals used/produced and the techniques employed in green chemistry are given below:

1. **Dry cleaning of clothes and laundry:** Formerly, tetracholoroethene ($Cl_2C=CCl_2$) was used as solvent for dry cleaning. This compound is suspected to be distraught and contaminated the ground water. Its use has been replaced by liquefied CO_2 along with a suitable detergent which is less harmful. Similarly, for bleaching of clothes in the laundry, hydrogen peroxide (H_2O_2) is being used which gives better results and is not harmful. Moreover, it saves a lot of water.
2. **Bleaching of paper:** Earlier, Cl_2 gas was used for bleaching paper which is highly toxic chemical. Its use has been transformed by H_2O_2 along with a suitable catalyst.
3. **In synthesis of chemicals:** For example, ethanal (CH_3CHO) is now-a-days being prepared on a commercial scale using environment friendly chemicals and conditions.

2. MATERIALS AND METHODS

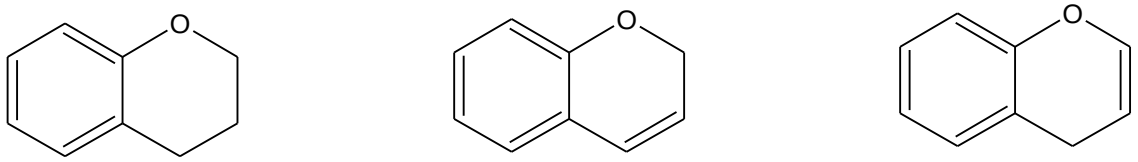
2.1 Solvent Free Reactions

Conventionally, chemical transformations have been carried out in a presence of a solvent to provide a homogenous medium for the reagent to interact effectively as well as for the dialysis and refining of the desired product [6]. Without the use of a solvent no reactions are possible and valid. It's enthralling that transformations and organic synthesis without solvents are industrially useful and largely ecological. The solvent-free reaction is a solvent-free chemical reaction system. In the 1990s 'supercritical fluids', have a remarkable history, their contribution as solvents for reactions really took off. Their characteristics could not be much apart from those of supercritical fluids, which are absolutely pressed gases displaying non-ideal phenomenon. Very differently, ionic liquids have vapor pressures so inclined to 0 that they can remain under ultra high-vacuum stage for lengthy duration with very small change from a liquid to a gas. Summative, these different version of solvents offer individual and familiar platform for both chemistry and in fact innovative scopes for manufacturing companies.

2.2 Heterocyclic Chromene Compounds

Heterocyclic frameworks are experienced in numerous gatherings of natural mixes having incredible pertinence in industry and additionally in our life in different ways i.e. the vast majority of the sugar and their subsidiaries, including vitamin C, e.g., exist to a great extent as five membered (Furanoside str.) or 06 members (Pyranoside str.) ring containing one O iota. The benzopyric nucleus consists some structural backbone such as 'chromene, chromene 2H and chromene 4H [7]'.

Biological active 4H-chromenes segments were derived by a 'one pot efficient, green, practical and environment friendly **multi component reaction (MCR)** of aromatic RCHO **(1**), Malononitrile (**2**) and RCOR′ derivatives (**3**)'. The method is very rapid, safe and avoids the use of hazardous and expensive reagents and solvents so this is a simple green and efficient term for synthesis of 4H-Chromenes derivatives. To decrease the fascination on ecologically operated chemicals, innumerable advantages to conduct reactions in aqueous basics. H_2O is the widest plentiful redemption solvent. Indeed, elixir is honoured as a fantasy aqua for many organic reactions [8]. Reactions in aqueous media/ Rochelle salt are significantly 'environmentally safe, impaired of any carcinogenic impressions, handle savvy, comparatively cheaper to operate, and especially features in industry.



Chromenes **2H-Chromene** **4H-chromene**

Fig. 1. Structures of Chromenes, 2H-Chromene, 4H-Chromene [2]

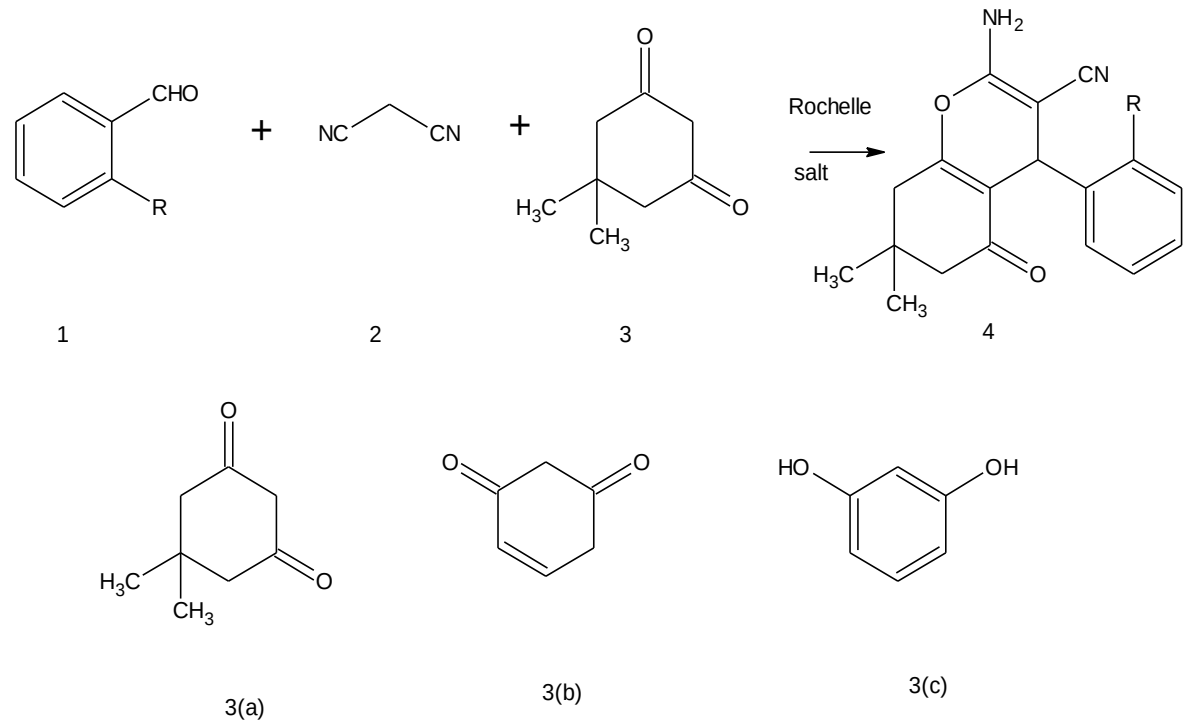


Fig. 2. Scheme for the synthesis of 4H-Chromenes derivatives [2]

2.3 Green Synthesis Approach

'Calea pinnatifida (R. Br.) Less.' is popularly known as "aruca", "cipó-cruz" or "quebra-tudo" or "Bitter Grass". Calea L. is a large genus of the 'Asteraceae family (tribe Heliantheae, subtribe Melampodiinae)', database marginally 125 species distributed essentially in tropical and subtropical areas. The leaves from *Calea pinnatifida* (R. Br.) Less., Asteraceae, were picked. Fresh analysing from *C. pinnatefida* (800 g) were extracted by camouflage for 15 days at room temperature with ROH 92%. After evaporation of the solvent under descending pressure, 12 g of the alcohol abstract of C. pinnatifeda were obtained.

To a mixture, an equimolar amounts of aromatic CHO (5 mmol), malononitrile (5 mmol) and 5,5-dimethyl-1,3-cyclohexanedione or resorcinol (5mmol) mixed in C_2H_5OH/water mixture (1:1) (10 ml) and Rochelle salt (30 g) was dissolved. The reaction blend was brought to reflux temperature for 2-4 hrs. After cooling to normal temperature, the targeted colloidal products were collected by filtration and dried [9,10].

3. RESULTS AND DISCUSSION

Over 03-quarters of the world population survived mainly on plants and adjunct extracts for personality care. Tentatively 30% of the entire plant rhythm, at one time or other was used for ecstatic purposes.

3.1 Biological Activity

1. ***'In vitro* antibacterial screening':** The curricula **4a-4f** were assessed contemplate *in vitro* antibacterial response against '*vibreocholerae*, *E. coli, B. subtilis, S. aureus* by the agar diffusion method, using Mueller-Hinton Agar' (Hi-media) medium [11,12]. Each compound was analyzed at a concentration of 100 µg/ml in DMSO. Ciprofloxacin was incorporated as the standard. The zone of inhibition (mm) was measured after 24 hrs incubation at 37°C.
2. ***'In vitro* antifungal screening':** The attachments **4a-4f** were observed for their *in vitro* antifungal activity against '*Chrysosporium sp., Trichoderma sp., A. niger, A. parasitica* by the agar diffusion method, using Sabouraud's dextrose agar' (Hi-media) media [13,14]. Each compound was tested at a concentration of 100 µg/ml in DMSO. Clomatrimazole was used as the template. The **zone of inhibition** was recorded after 24 hrs incubation at 37°C.
3. **Antibacterial Activity:** The bacterial radius of inhibition statistically (mm) are represented in Table 2. The antimicrobial

activities of multifunctional '*Vibreocholerae, E. coli, B. subtilis, S. aureus'* were screened. Ciprofloxacin were used as an authorized at 100 µg/ml.

Concoctions **4a-4f** was winnowed. ***Vibreocholerae*** for curriculum **4b** was incredulous dominantly active compared with the reference ciprofloxacin. On the other hand, for compound **4a, 4c, 4d** had little activity compared with the ciprofloxacin and for compound **4f** shows passivity. ***E. coli*** for compound **4f** was found to be soundly active, on the other hand for compound **4a-4e** had weak activity compared with the ideal ciprofloxacin. ***B. subtilis*** for compound **4c** was found to be strongly active compared with the ciprofloxacin [15-17]. On the other hand for **4a, 4b, 4d, 4e, 4f** had feebly activity compared with the ciprofloxacin. ***S. aureus*** for compound **4d** was found to be highly active compared with ciprofloxacin on the other hand for compound **4a, 4b, 4c, 4e, 4f** had scarce activity compared with the ciprofloxacin.

4. **Antifungal Activity:** The fungal zones of inhibition mathematically (mm) are summarized in Table 3. The antifungal activity of aftermaths '*Chrysosporium sp., Trichoderma sp., A. niger, A. parasitica'* were screened. Clomatrimazole were used as a standard at a 100 µg/ml. Compound **4a-4f** were screened. **Chrysosporium sp**. for compound **4c** was found to be too active in comparison to Clomatrimazole while on the other hand for compound **4a, 4b, 4d, 4e, 4f** had passivity compared with standard Clomatrimazole.

Table 1. Comparative study of products (in term of their yield & M.P.) obtained by changing the R-group [2]

Entry	Products M.F.	R	*3*	Reaction time (hrs)	*Isolated yield (%)*	*M.P. (°C)*
4a	$C_{17}H_{17}N_3O_4$	*p*-NO_2	**3a**	2-4	90%	220-222
4b	$C_{20}H_{23}N_3O_2$	*p*-$N(CH_3)_2$	**3a**	2-4	92%	209-201
4c	$C_{18}H_{16}N_2O_3$	*p*-CH_3CO	**3b**	2-4	90%	198-200
4d	$C_{16}H_{12}N_2O_2Cl_2$	*o*-Cl, *p*-Cl	**3b**	2-4	88%	192-194
4e	$C_{18}H_{14}N_2O_4$	*p*-OH,*m*-CH_3CO	**3c**	2-4	95%	240-242
4f	$C_{16}H_{11}N_2O_2$	-	**3c**	2-4	90%	234-237

Table 2. Antibacterial activity of compounds (synthesized chromenes derivatives (4a-4f) [2]

Compound	Concentration of compound (µg/ml)	ZOI of sample			
		Vibreocholerae	*E. coli*	*B. subtilis*	*S. aureus*
4(a)	100	22	16	14	15
4(b)	100	30	16	7	9
4(c)	100	22	17	18	13
4(d)	100	12	15	15	25
4(e)	100	12	25	14	13
4(f)	100	-	27	16	15
Ciprofloxacin	100	32	27	21	24

Table 3. Antifungal activity of compounds (synthesized chromenes derivatives (4a-4f) [2]

Compound	Concentration of compound (µg/ml)	ZOI of sample			
		Chrysosporium sp.	*Trichoderma sp.*	*A. niger*	*A. parasitia*
4a	100	15	10	13	17
4b	100	9	-	10	8
4c	100	24	11	17	20
4d	100	15	15	22	16
4e	100	20	20	24	16
4f	100	15	15	26	18
Clomatrimazole	100	25	27	24	27

Trichoderma sp. for contrivance **4e** was observed to be very dynamic then again for compound **4a, 4c, 4d, 4f** had low movement contrasted and standard Clomatrimazole. While for compound **4b** had no labeling with Clomatrimazole. ***A. niger*** for compound **4e** was traced to be embellishing contrary with standard Clomatrimazole [15-17]. Alternatively for **4a, 4b, 4c, 4d, 4f** had dormancy compared with standard Clomatrimazole. ***A. parasitica*** for compound **4c** was aligned extreme active compared with stationery Clometrimazole. The frightening thing for **4a, 4b, 4d, 4e, 4f** had deficient activity compared with Clomatrimazole.

4. CONCLUSION

Apparently, traditional procedures for the preparedness of chromenes derivatives are found to be disgusting because of less adherences and yield. So the most handholding method for the synthesis of these compounds is the MCRs. The basic resources of medicines come from nature and they are used as medicaments from archaeological to robotics day. Thus, by green chemistry, we mean producing the particulates of our needs using such reactions and chemical processes which neither use disappoint *Rasayan* nor progression such contaminants into the atmosphere. Although it is a fascinating task but some beginner efforts have already been made to achieve this goal.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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