Heterocyclic Letters
Vol. 11| No.1|111-130| Nov-Jan |2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SHORT REVIEW ON PHARMACOLOGICAL CHARACTERISTICS AND SYNTHESIS OF PYRAZOLE

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Abstract. Pyrazole possesses pharmacological activities such as antidepressant agent e.g.fezolamide, analgesic e.g.betazole, a H2-receptor agonist e.g.celecoxib, difenamizole, the anti-obesity drug e.g..rimonabant, So the pyrazole nucleus attract attention of researchers to study biologically and chemically skeleton of pyrazole nucleus, this review show pharmacological activity ,synthesis and biological activity of heterocyclic compounds containing pyrazole nucleus ..

Keywords: Pyrazoles, Synthesis, Pharmacological characteristics, therapeutic activities..

Introduction

Pyrazoles are five-membered heterocycles that institute a class of composites mainly beneficial in organic creation. They are one of the greatest studied collections of composites between the azole families. Actually, an enormous variability of synthesis ways and synthetic correspondents have been stated over the years. The existence of the pyrazole nucleus in altered constructions indicates to varied implementation in altered areas as technology, medication and agriculture. Especially, they are pronounced as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, antiinflammatory, anti-tuberculosis, antioxidant in addition to antiviral causes [I, II]. Currently, pyrazole systems, as biomolecules, have involved more care because of their remarkable pharmacological characteristics. This heterocycle can be found in a number of well- recognized drugs pertinence to altered types with different healing actions (Figure 1) [III–X].

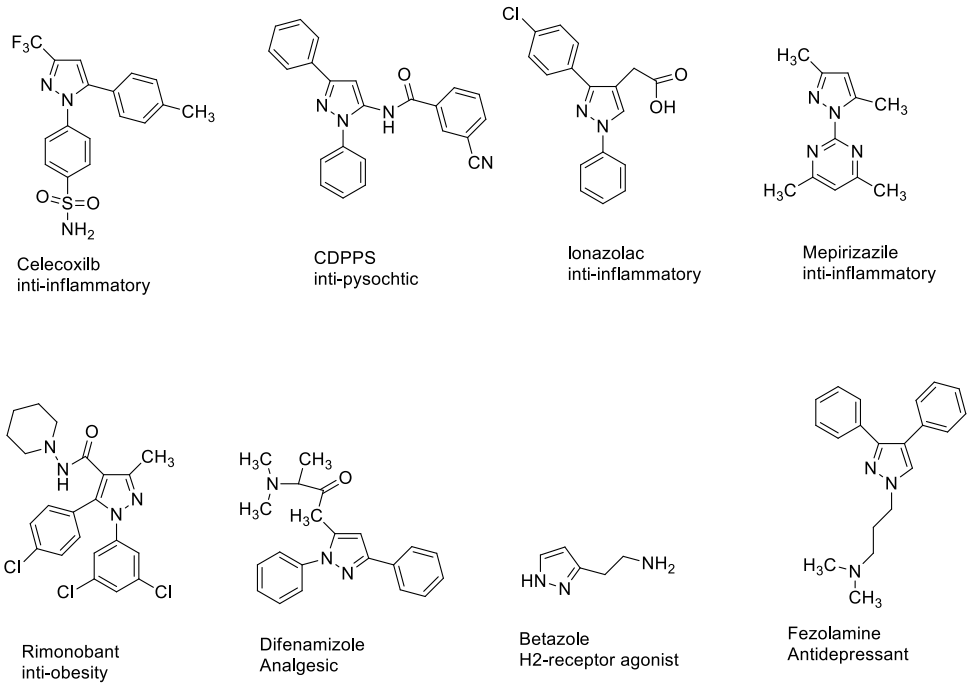


Figure1: pharmaceutical drugs containing pyrazole Unit.

Many research program [XI–XXV], are pointing to combine chemical constructions of significant pharmacophoric influences for advancing their healing abilities, in specific in contradiction of extreme sicknesses. one of this program pointing at merger pyrazole, thiazole, and 1, 2, 4-triazole moieties in lone construction. Recently, attention in pyrazole chemistry has very improved primarily because of the detection of a huge variety of interesting pyrazole-based drugs, for example, apixaban, fipronil, tolpiprazole, etabonate, celecoxib, remogliflazone, lonazolac, deracoxib, ruxolitinib, and crizotinib[XXVI–XXXI], as shown in Figure 2. As second moiety in this preface, thiazole has an extreme constituent influence of the pharmacophores of an extensive number of therapeutic importance molecules for example antibacterial [XXXII], antiprotozoal [XXIII], and antifungal activities [XXXIV, XXXV]. Furthermore, synthetic thiazoles were broadly examined and recognized as antiproliferative causes [XXXVI–XXXVIII], and apoptosis-inducing [XXXIX] and cell division stopping capacities were stated as anticancer activity method [XL]. Lastly, as third theme in this introduction, triazole and its derivatives hold an energetic session of biologically and pharmacologically active heterocyclic compounds for example antibacterial [XLI]. Presently, investigators continue to enterprise and manufacture new 1, 2, 4-triazole and 1, 3, 4- thiadiazole analogs because of their high antimicrobial activity towards a varied range of gram-positive and gram-negative bacteria and yeasts. 1, 2, 4-Triazole derivatives are still intensively considered as they own strong antifungal possessions [XLII]. Newly, 1, 2, 4-triazole annulated composites were conveyed as possible anticonvulsant [XLIII–XLV] and anti-HIV causes [XLVI, XLVII]. Moreover, a huge number of synthesized 1,2,4-triazole analogs have been informed with important antibacterial, antifungal, antiviral, antituberculosis, anti-inflammatory, anticonvulsant, antidepressant, and anticancer actions [XLVIII–L].

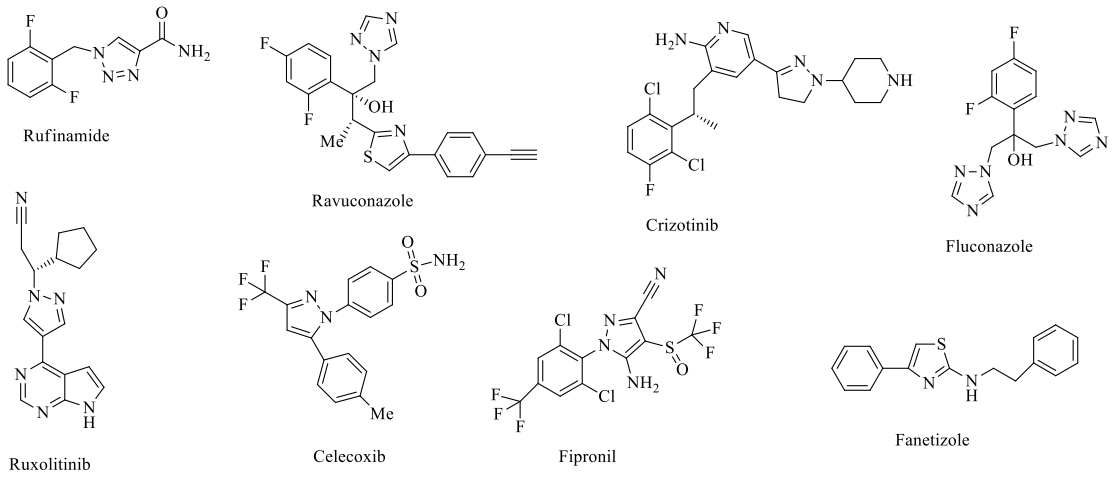
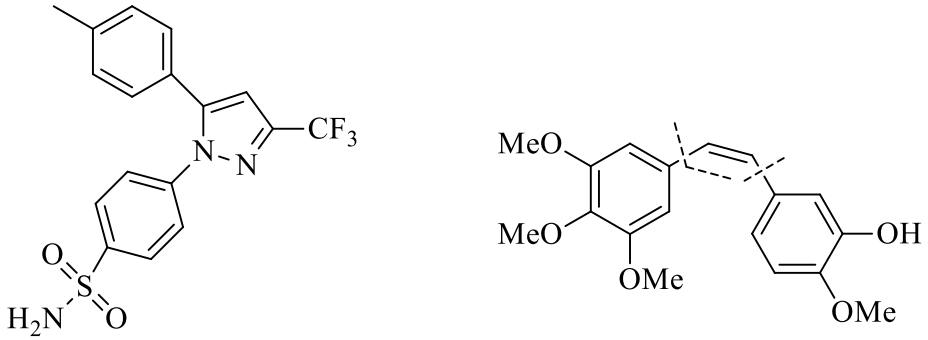


Figure2: Representative examples of biologically active pyrazole, triazole, and thiazole derivatives.

Synthesis of pyrazole derivatives and their pharmacological active

From a remedial chemistry viewpoint, the cis-diphenylethylene scaffold characterizes an advantaged constructions thoroughly examined. Celecoxib (Celebrex®, Onsenal®), a 1, 5-diphenylpyrazole derivative comprising cis-diphenylethylene scaffold, creates a strong and definite inhibitor of the human cyclooxygenase-2 (COX2; Figure **3**).



Celecoxib(1) Combretastatin A-4 (2)

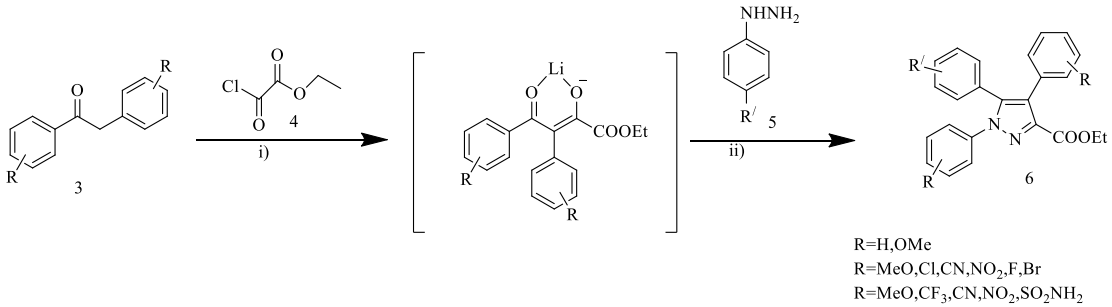
Figure3: Structure of Celecoxib (1) and Combretastatin A-4 (2)

Celecoxib has been revealed to be effective in pain and arthritis in humans lacking several of the possibly severe poisonousness related with traditional NSAIDs. COX-2 is likewise constitutively overexpressed in numerous human premalignant, malignant and metastatic epithelial tumors, e.g., colorectal, lung, breast, prostate and head/neck cancer [LI–LIV]. Preclinical studies revealed promising antitumor action of celecoxib in variation of human tumors [LV–LIX]. It has been accepted for oral usage in the inhibition of colon cancer growth in patients with FAP. Though, it was exposed that celecoxib and related compounds may encourage cell cycle stop, apoptotic cell death, prevent tumor development, and destroy tumor neo-angiogenesis in the lack of any visible participation of COX-2 [LX–LXII]. The two pharmacologic influences, inhibition of COX-2 and elimination of tumor development, were realized to exist in different structural features of the celecoxib molecule. These conclusions create celecoxib an attractive indicating compound for evolving new anticancer causes [LXIII–LXVI]. Combretastatins, a family of stilbenoids from the South African willow tree Combretumcaffrum (ECKL. &ZEYH.) KUNTZE (Combretaceae), are also distinguished by the existence of 1, 2-diphenylethylene nucleus and have develop of specific attention to

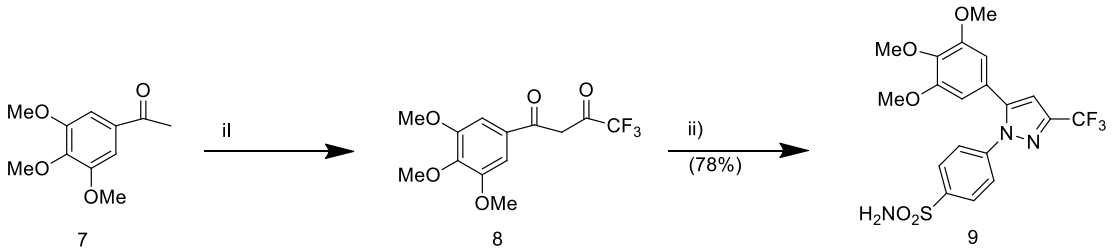
chemists and biologists due to their extensive series of biological actions comprising anti-inflammatory, anticancer, antiviral, antioxidant and additional newly neuroprotective impacts (Figure **3**) [LXVII]. Combretastatin A-4 (CA-4) reveals potent antitubulin action by coercing to the colchicine coercing site of tubulin [LXVIII]. It shows strong cytotoxicity contrary to a varied spectrum of human cancer lines. The multiple biological actions and the structural simplicity of combretastatin products cause them appropriate for the scheme of hybrid medicines and numerous specimen of stilbene based hybrid compounds as possible causes in the arenas of cancer, anti-inflammation and other related illnesses have been conveyed in the last decade [LXVII]. the production and biological actions of aryl-substituted pyrazole products mimicking cis-diphenylethylene scaffold of celecoxib in addition to CA-4. The cytotoxic influences of these mixtures contrary to three human cancer cell lines HT29, Hep-G2, MCF-7 in addition to the inhibition of NO creation by lipopolysaccharide (LPS)-stimulated murine macrophage RAW 264.7 cells were examined. The responsibility of NO in tumor biology is complex, for the reason that it has both facilitators and inhibitory parts in cellular procedures dependent on the circumstances, so NO inhibition is directly unconnected to the cytotoxicity [LXIX]. But NO exhibitions a variation of the similar beneficial pharmacological properties as prostaglandins in the cardiovascular system comprising vasodilation, inhibition of platelet collection, modulation of platelet and leukocytes adherence to vessels [LXX]. The usage of selective COX-2 inhibitor celecoxib in chemoprevention of breast cancer and other malignancies has been limited by its adversative effects, in specific the danger of cardiovascular actions mainly associated to their capability to decrease the creation of prostacyclin PGI2 [LXXI]. Based on the opinion that keeping of NO creation together with coxib- stimulated actions thus might aid preventing danger of cardiovascular toxicity, a strategy to originate a multi-target drug via joining COX-2- selective inhibition with nitric oxide (NO)-dependent actions has been started [LIX,LXXII,LXXIII].

The hybridization strategy to join the significant pharmacophoric groups of two original composites celecoxib and CA-4 in a single molecule. usage of 1, 2-diphenyl replaced pyrazolecircle of celecoxib as a scaffold to mimic the cis-1, 2-diphenylethylene motif in CA-4. Substitute of the double bond with heterocyclic five-membered circles was established to preserve both cytotoxic and antitubulin actions of the composites [LXXIV]. Actually, these cis-locked analogs deliver numerous benefits: avoiding of isomerization from cis to trans; growing specificity of these medicines to cellular targets; and advancing the healing possible of these medicines. The occurrence of the trimethoxybenzene moiety of CA4 is too vital to gain appropriate cytotoxic and antitubulin answers [LXXV]. The mainly concerned in keeping the sulfonamide group or associated bioisosteres of celecoxib which looks to cause its COX-2 selectivity [LXXVI]. The COX-2 inhibitory influence, if any, will participate to the whole antitumor action of new molecules. An one-pot approach has been utilized to make a diversity of ethyl 1,4,5-triaryl-1H-pyrazole-3-carboxylates in moderate to high produces from ethyl oxalyl chloride, 1,2-diarylethanones and arylhydrazine hydrochlorides (**Scheme 1**) [LXXVII]. The t BuOLi mediated Claisen condensation of 1, 2-diarylethanones and ethyl oxalyl chloride effectively supplied the enolized lithium salts of ethyl 2, 4-dioxo-3, 4-diarylbutanoates, which in situ re-joined with arylhydrazine hydrochlorides through a hydrochloric acid-promoted Knorr reaction to yield the exquisite triarylpyrazole-3-carboxylates. A procedure for the preparation of celecoxib was too used (**Scheme 2**). 3, 4, 5-Trimethoxyphenyl-1, 1, 1-trifluoro-2, 4- butanedione gained from a Claisen concentration between acetophenone products and ethyl trifluoroacetate thereby re-join with 4-sulfamidophenyl hydrazine halide salt to make the 3, 4, 5-trimethoxyphenyl analog of celecoxib. Cytotoxicity of the synthesized compounds and celecoxib were assessed for their inhibition rate of cell development contrary to three human

tumor cell lines (HT-29, Hep-G2 and MCF-7) by a method advanced by [LXXVIII]. The antiproliferative action of celecoxib on human breast cancer cells (MCF-7), human hepatocellular carcinoma cell (HepG2) and human colorectal cancer cells (HT-29) were alike to those formerly available [LV, LXXIX, LXXX].



Scheme 1. Synthesis of ethyl 1,4,5-triaryl-1H-pyrazole-3-carboxylates 6. Reaction conditions: i) Ethyl oxalyl chloride 4 (1 equiv.), 3 (1.0 mmol), tBuOLi (2.5 equiv.) in anhydrous THF (5 mL), for 6 h under reflux then remove THF. ii) EtOH (5 mL), concentrated HCl (1.0 equiv.), arylhydrazine hydrochlorides 5 (1.0 mmol) for 6 h under reflux. Products 6 were isolated by column chromatography.



Scheme 2.Synthesis of 3, 4, 5-trimethoxyphenyl analog of celecoxib. Reaction conditions: i) **7** (0.21 g, 1.0 mmol), ethyltrifluoroacetate (0.18 g, 1.3 mmol), NaH (0.03 g, 1.2 mmol) in THF (5 mL), 50°C for 2 h. ii) Trifluoroacetic acid (0.18 g, 1.6 mmol), 4-sulfonamidophenylhydrazine hydrochloride (4-SAPH · HCl; 23.0 g, 1.0 mmol) at 55°C for 1 h.

Microbial pollutions in humans have penetrated the worrying stages through the world particularly with the increase of multidrug resistant pathogens which has moreover decreased the efficiency of the obtainable arsenal of antibiotics [LXXXI, LXXXII]. This has necessary the search for novel constructions presenting broad-spectrum antibacterial and antifungal characteristic. Especially, fungal contaminations produced by the most public fungal pathogens, Candida albicans, Cryptococcus neoformans, and Aspergillusfumigatus, pose a severe risk to immunocompromised patients [LXXXIII]. Amongst all these fungal pathogens, C. albicans is one of the prevalent cause producing nosocomial pollutions which are associated through biofilm development on indwelling medicinal tools (e.g., ocular lenses, catheters, heart valves, dental implants, vascular bypass grafts, artificial joints, and central nervous system shunts) [LXXXIV, LXXXV] C. albicans shows dimorphic development array in the nature (i.e., planktonic and biofilm) [LXXXVI]. Biofilm cell populations of diverse Candida spp. such as C. albicans, Candida glabrata, Candida krusei, and Candida parapsilosis are relatively resistant to different antifungal causes as amphotericin B, nystatin, clotrimazole, fluconazole, voriconazole, miconazole. Correspondingly, Aspergillusfumigatus biofilms are relatively resistant to itraconazole and to certain degree caspofungin[LXXXVII].

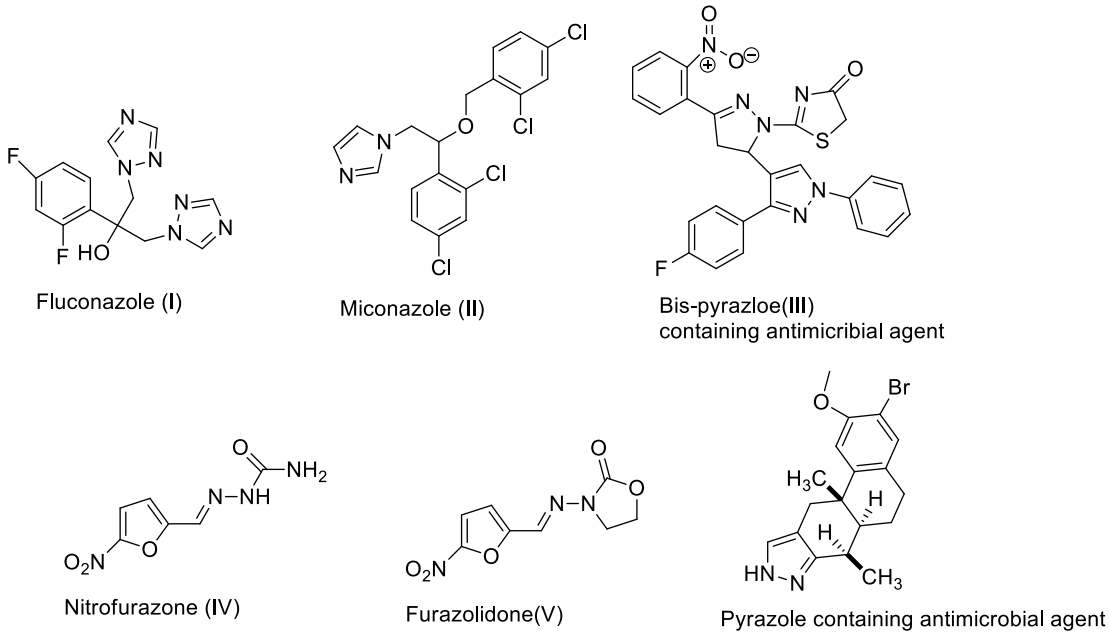
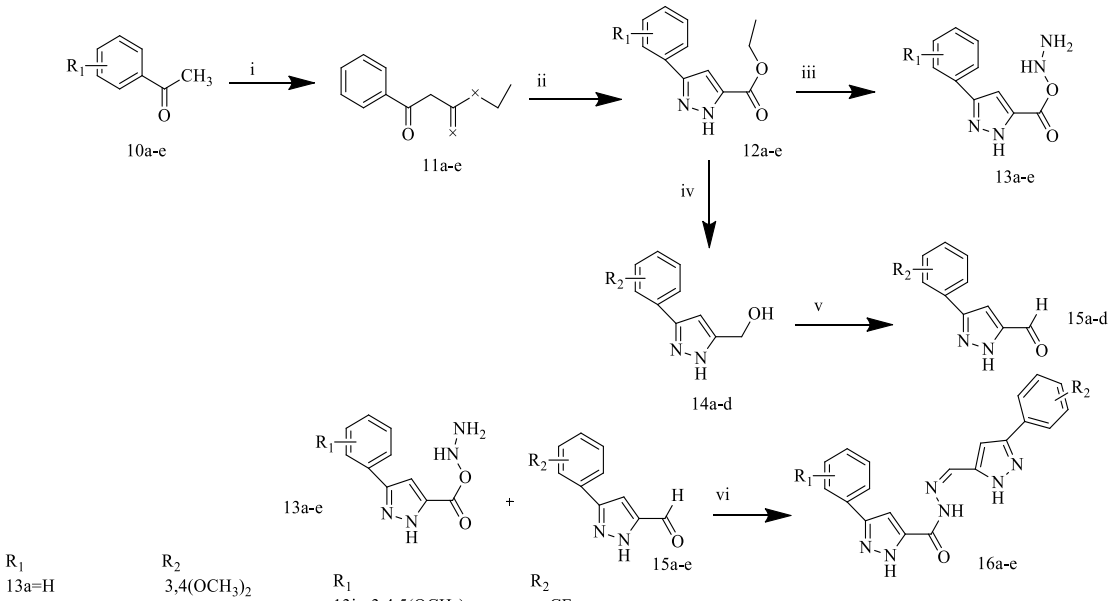


Figure 4: Structures of some antimicrobial agents.

The mortality rate because of fungal contaminations is over 1.35 million per annum, in spite of the obtainability of four changed types of chemotherapeutic antifungal medicines and between them azole comprising drugs [fluconazole (Figure **4**), itraconazole, voriconazole, miconazole, and posaconazole] is broadly useful as first line antifungal treatment that roles by stopping the fungal lanosterol 14α demethylase (CYP51) through binding among nitrogen of azole to the heme iron atom in the binding place of enzyme [LXXXVIII, LXXXIX, XC], while the inhibition of lanosterol outcomes in the interfering in the role of ergosterol as a membraneconstituent and plasma membrane interruption that change the actions of numerous membrane- bound enzymes [XCI].

On the other hand, greatest of the azole medicines have revealed limitation in terms of their drug resistance, narrow antifungal spectrum, and little bioavailability in practical appliances [XCII]. Seeing these truths, there is a critical importance to detect novel azole antifungal causes revealing strong broad-spectrum action, low poisonousness, and low resistance. Pyrazole is one of the advantaged construction from azole family and is presently acquiring renewed care as a possible biomolecule in view of its interesting pharmacological characteristic comprising antimicrobial [XCIII], anticancer [XCIV], analgesic [XCV], antihyperglycemic [XCVI], anti-inflammatory [XCVII], antihypertensive [XCVIII], CNSlike activity, antidepressant [XCIX]; however, the possible of pyrazoles as antifungal causes is still not discovered to a bigger degree. Hydrazide is gained from oxoacids, in which –OH is substituted by –NRNR2 (R groups are commonly H), as in carbohydrazides, RC (=O) $NHNH_2$; sulfonohydrazides, RS (=O) $2NHNH_2$; and phosphonicdihydrazides, RP (=O) ($NHNH_2$). Hydrazide has attracted care of therapeutic chemists in opinion of their varied range of biological actions as antibacterial, antifungal, anticonvulsant, anti-inflammatory, antimalarial, and anti-tuberculosis [C, CI, CII, CIII, CIV, CV, CVI, and CVII]. Prompted by the above-mentioned discoveries and in continuance of our continuing study on the creation of bioactive conjugates [CVIII, CIX], the preparation of hybrid products including of two replaced pyrazole moieties (**Scheme3**) combined via a hydrazide linker and later assessed their antibacterial, anti-Candida, and anti-biofilm actions. Additional, mechanistic characteristics of the suggesting indications on ergosterol biosynthesis inhibition in dissimilar C. albicans strains were recognized, which were further confirmed via molecular docking revisions [CIX]



R_1	R_2
13a=H	$3,4(OCH_3)_2$
13b=H	$3,4,5(OCH_3)_3$
13c=H	CF_3
13d=H	$3,4(OCH_2O)$
13e=OCH_3	$3,4(OCH_3)_2$
13f=OCH_3	$3,4,5(OCH_3)_3$
13g=OCH_3	CF_3
13h=OCH_3	$3,4(OCH_2O)$
13i= $3,4,5(OCH_3)_3$	$3,4,5(OCH_3)_3$

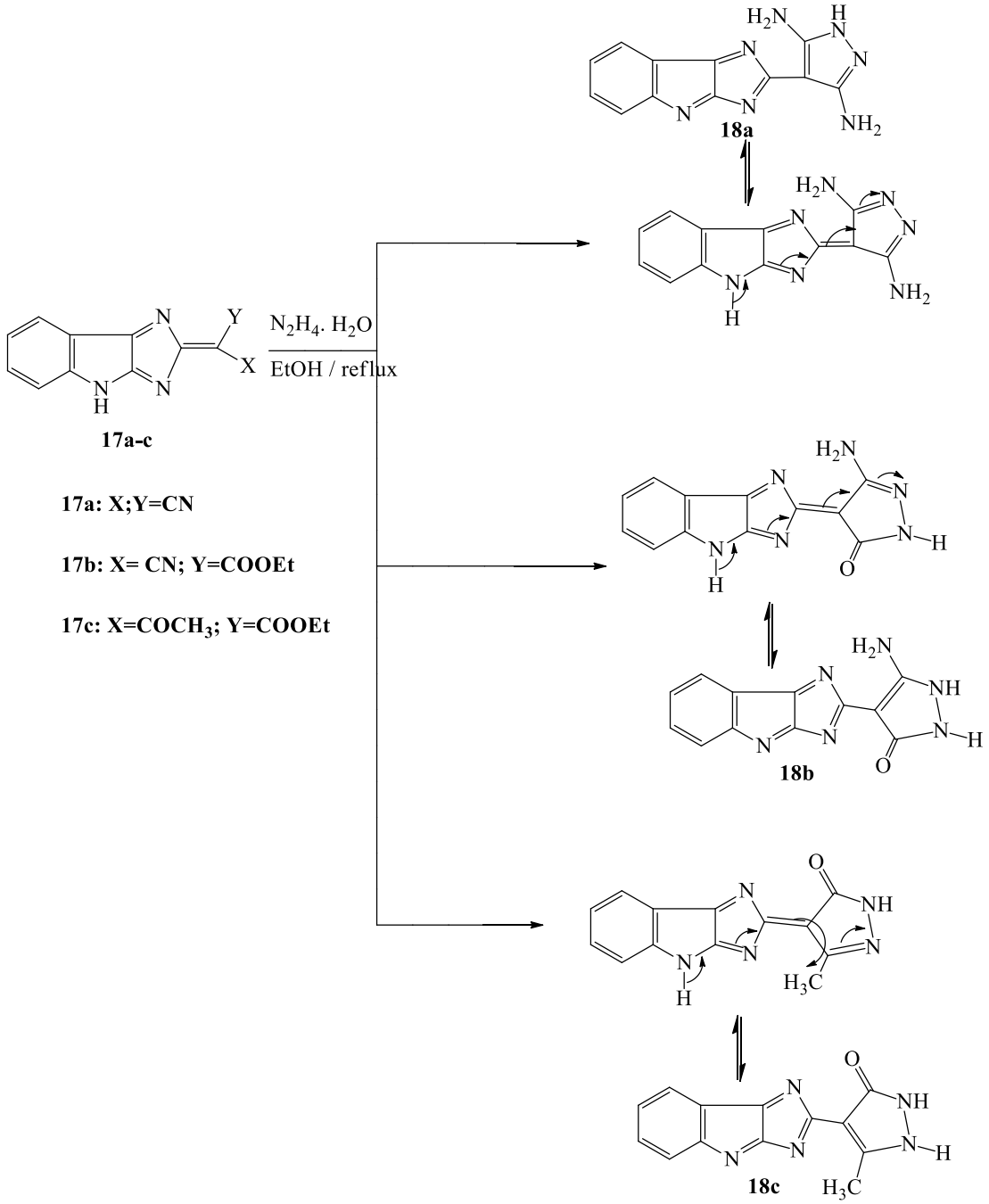
R_1	R_2
13j= $3,4,5(OCH_3)_3$	CF_3
13k=$3,4,5(OCH_3)_3$	$3,4(OCH_2O)$
13l=CF_3	$3,4(OCH_3)_2$
13m=CF_3	$3,4,5(OCH_3)_3$
13n=CF_3	CF_3
13o=CF_3	$3,4(OCH_2O)$
13p=$3,4(Cl)_2$	$3,4(OCH_3)_2$
13q=$3,4(Cl)_2$	$3,4,5(OCH_3)_3$

R_1	R_2
13r=$3,4(Cl)_2$	CF_3
13s=$3,4(Cl)_2$	$3,4(OCH_2O)$

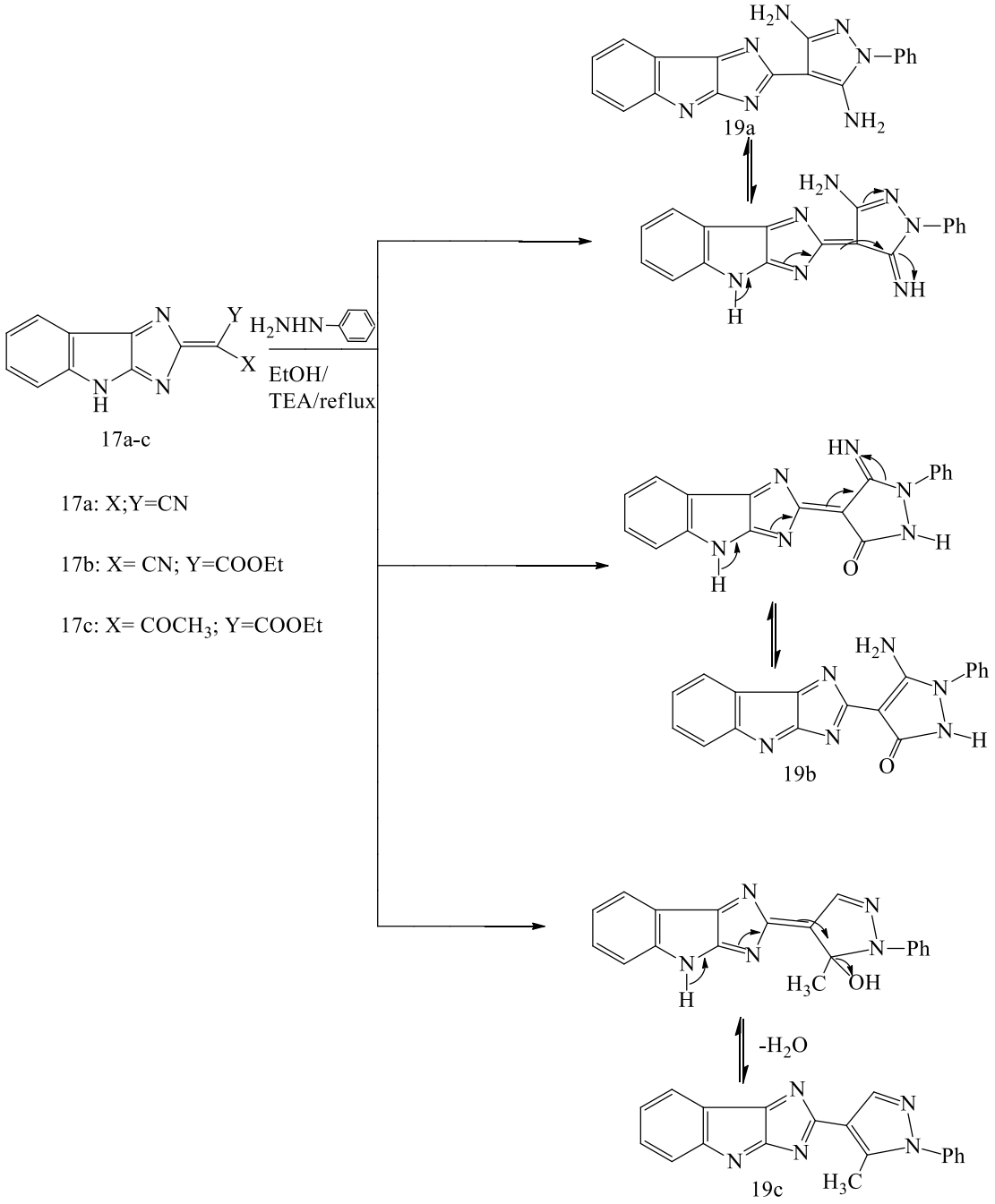
Scheme 3.Synthesis of bis-pyrazolehydrazide derivatives16 (a–e). Reagents and conditions: (i) Diethyloxalate, NaOEt/Ethanol, 0°C-rt, 4 hr; (ii) N2H4·2HCl/ethanol, reflux, 3–4 hr; (iii) N2H4·H2O/ethanol, reflux, 3–4 hr; (iv) LiAlH4/THF, 2 hr, 0°C-rt; (v) IBX/dryDMSO, 1 hr, rt; (vi) EtOH, glacial acetic acid.

New pyrazole, having imidazo[4,5-b]indol moiety were effectively created(**Scheme 4,5**) and assessed as probable antimicrobial causes. [CX].

Novel pyrazole, imidazole, pyrimidine products were measured for their antibacterial activities and in vitro antifungal. These created composites could get effective appliances as antibacterialand antifungal causes in pharmaceutical [CX]

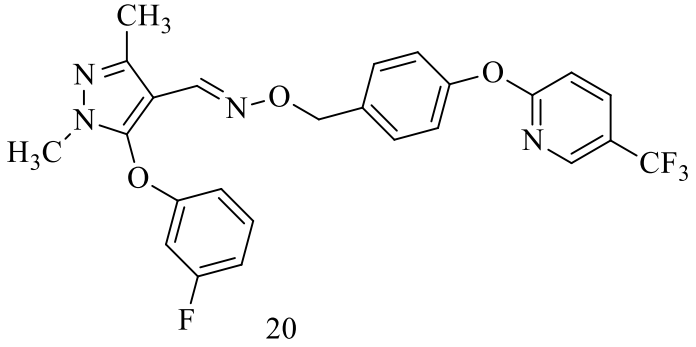


Scheme 4.Synthetic routes for the compounds **18a-c**.



Scheme 5.Synthetic routes for the compounds **19a-c**.

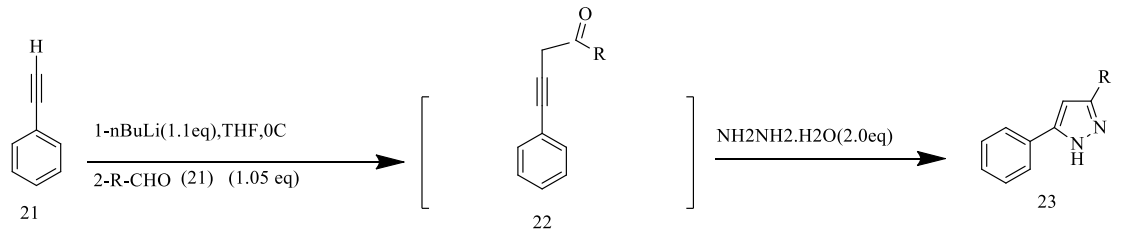
The sequence of pyrazoleoxime products comprising a 5-trifluoromethylpyridyl moiety were produced and determined for their insecticidal and acaricidal actions .The results of compound (**20)** (Figure.**5**) show excellent acaricidal action in contradiction of T. cinnabarinus and showed possible insecticidal action in contradiction of P.xylostella and A. craccivora [CXI]



20

Figure 5: Pyrazole derivatives with pesticidal activity

Reaction of terminal alkynes (**21)** and aromatic aldehydes (**22)** in presence of hydrazines and, molecular iodine afford the corresponding 3, 5-substituted pyrazole(**23)** .the yield arrange between (68–99%) (**Scheme 6**) [CXII]

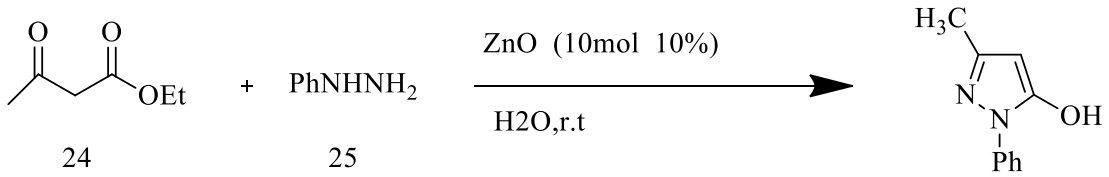


21 22 23

R=Ph,4-MeOPh,4-MePh,2-MePh,3-MePh,4-Cl,4-CF_3Ph

Scheme 6: Synthesis of pyrazole from α,β-unsaturated carbonyl and hydrazine

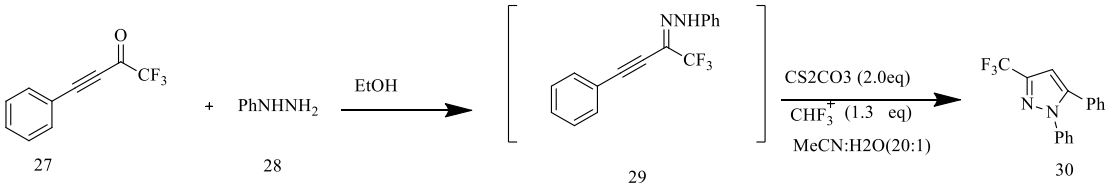
Treatment of ethyl acetoacetate (**24**) with phenylhydrazine**(25**) in presence of nano-ZnO catalyzed provide 1, 3, 5-substituted pyrazoles derivatives (**26**) with excellent yield (95%) (**Scheme 7**) in short time and easy work-up procedure. [CXIII]



24 25 26

Scheme 7.Synthesis of 1, 3, 5-substituted pyrazoles from ethyl acetoacetate.

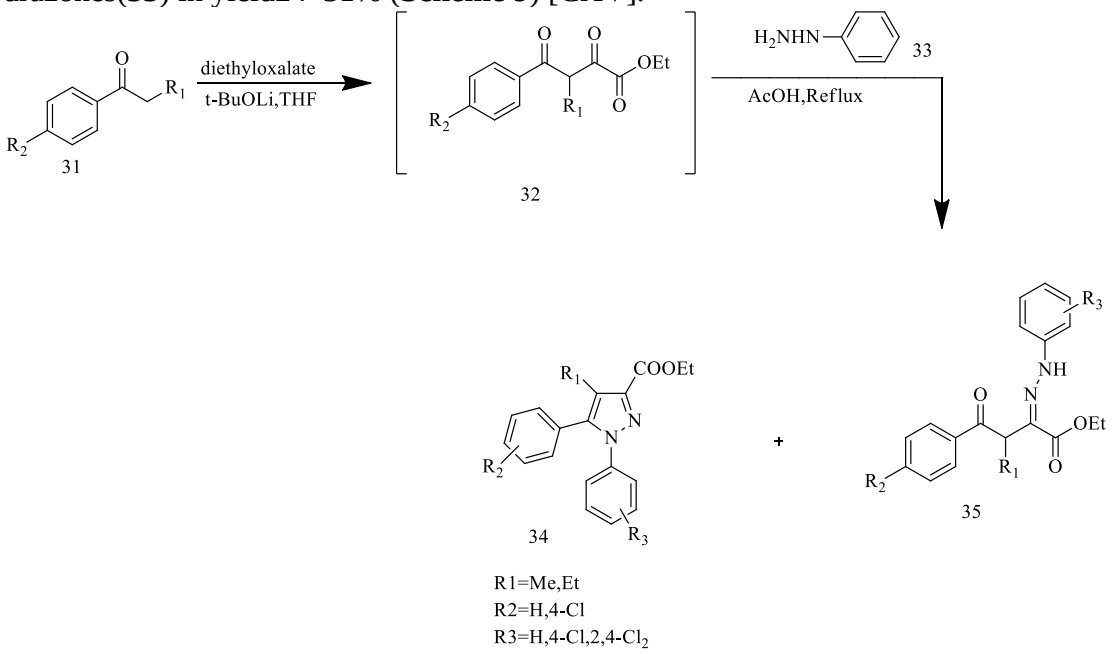
Reaction of acetylenicketones(**27**)with phenylhydrazine(**28)** and hypervalent iodine reagent under transition-metal-free conditions afford the corresponding 3-trifluoromethylpyrazoles(**30**) with good yields(**Scheme8**)[CXIV]



27 28 29 30

Scheme 8.Synthesis of 3-trifluoromethylpyrazoles via cyclization of acetylenic ketones.

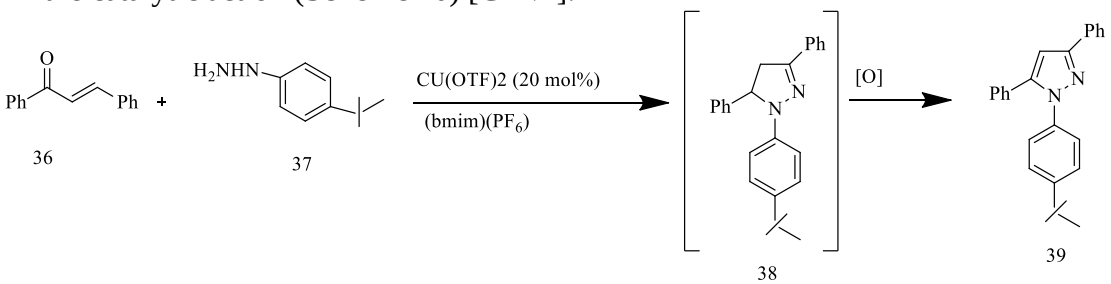
Treatment of arylhydrazine(**33**) with carbonyl products (**32**) which was set in situ from acetone (**31**)which was changed to 1,5-isomers (**34**) in the yields of 60–66%. Meanwhile, N-arylhydrazones(**35**) in yield24–31% (**Scheme 9**) [CXV].



31 32 34 35

Scheme 9.Synthesis of pyrazole via cyclocondensation reaction of 1, 3-dicarbonyl and arylhydrazine

Reaction of α,β-ethylenic ketone (**36**) with p-(4-(tert-butyl) phenyl)hydrazine (**37**) and mixture of copper triflate and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim] (PF6) as stimuli, afford pyrazoline(**38**) which followed by oxidation in situ to give . 1,3,5-trisubstituted pyrazole(**39**) in good yields (about 82%) ,the response procced through cyclocondensation among chalcones and arylhydrazines, and oxidative aromatization stands without the requisite of an extra oxidizing reagent. The catalyst can be reused more than four cycles without much loss in the catalytic action (**Scheme 10**) [CXVI].



36 37 38 39

Scheme 10.Synthesis of pyrazoles45 from α, β-ethylenic ketone.

Conclusion

Pyrazole own various biological activities and pharmacological properties,the modification of the preparation of basic pyrazole lead to the synthesis of new derivatives with biological

activity, also pyrazole exhibit anti-inflammatory, anti-cancer properties , analgesic, antimicrobial, and used for therapeutic purposes.

Acknowledgments

The financial support from Jouf University, Saudi Arabia, and Aswan University, Aswan, Egypt is gratefully acknowledged. The authors declare no conflict of financial, academic, commercial, political, or personal interests.

Conflicts of Interest: The authors declare no conflict of interest

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Received on September17, 2020.