Accepted Manuscript

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PII: S0223-5234(19)30488-X

DOI: https://doi.org/10.1016/j.ejmech.2019.05.070

Reference: EJMECH 11380

To appear in: *European Journal of Medicinal Chemistry*

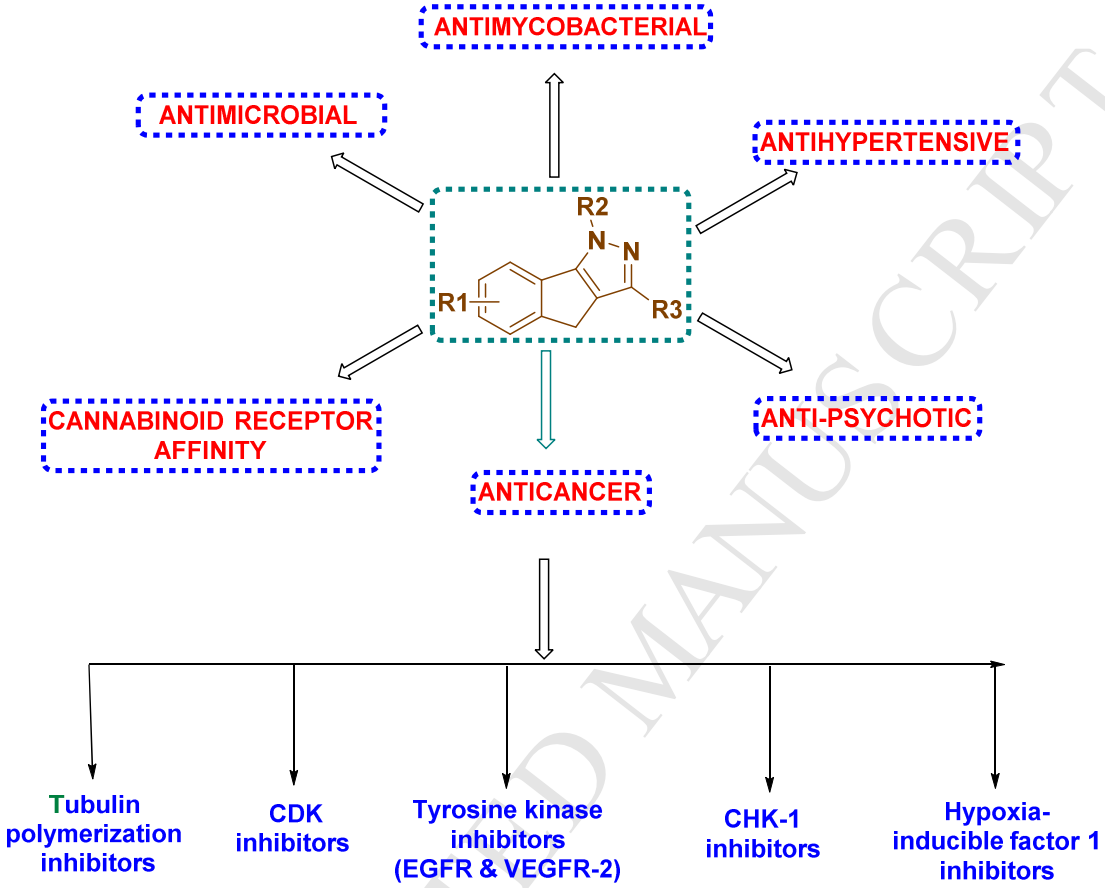
Received Date: 23 March 2019

Revised Date: 25 May 2019

Accepted Date: 25 May 2019

Please cite this article as: I. Khan, M.A. Shareef, C.G. Kumar, An overview on the synthetic and medicinal perspectives of indenopyrazoles, *European Journal of Medicinal Chemistry* (2019), doi: https://doi.org/10.1016/j.ejmech.2019.05.070.

Graphical abstract



An overview on the synthetic and medicinal perspectives of indenopyrazoles

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Abstract

Indenopyrazole is emerging as one of the most promising and privileged scaffold in medicinal chemistry. This scaffold have been investigated for the development of novel derivatives and hybrids with other moieties and substituents exhibiting a wide range of medicinal properties like antimycobacterial, antipsychotic, antihypertensive, cannabinoid receptor affinity, anti-tumor, antimicrobial, etc. Furthermore, indenopyrazoles function as inhibitors in various mechanistic pathways which has been well established based on its anticancer potential. This review illustrates various synthetic strategies adopted and reveals the extensive significant biological properties of indenopyrazoles. Furthermore, ample scope is available for this scaffold which needs to be explored by medicinal chemists for the development of new potential drug candidates.

Keywords: Indenopyrazole; antimycobacterial; antipsychotic; antihypertensive; antitumor

1. Introduction

From the perspective of design and discovery of new pharmacologically active molecules, the synthesis of heterocyclic ring containing compounds holds a pivotal role in organic and medicinal chemistry as its helps in bridging life sciences with biochemical investigations [1-3]. Currently, around 60% of the top retail selling drugs have at least one heterocyclic nucleus as part of the overall drug since it provides the scaffold with an improved solubility and salt formation properties which helps in oral absorption and bioavailability as well as it helps in arranging the pharmacophore to develop potent and selective drugs [4-6]. Boyd in 1965 was the first chemist who synthesized and reported indenopyrazole as a new pseudoazulenic system having fused two five-membered rings [7]. Indenopyrazole is a three fused ring compound containing two five membered and one six membered rings, wherein the 3rd ring is a pyrazole ring having two nitrogen atoms adjacent to each other exhibiting tautomerization of the proton. Subsequently, Lemke and co-workers [8] in 1978 reported for the first time that indenopyrazoles can function as antipsychotic agents, later this scaffold has gained a renewed interest among medicinal chemists since new molecular hybrids were generated based on chemoinformatic approaches and diverse synthetic strategies and these indenopyrazole derivatives exhibited other pharmacological and bioactivities such as antimycobacterial, antipsychotic, antihypertensive, cannabinoid receptor affinity, antimicrobial and anticancer.

2. Synthetic strategies

Indenopyrazole has a pyrazole ring that provides almost similar synthetic routes of pyrazole. Similarly, the 3rd position of pyrazole ring in the indenopyrazole system is available for the nucleophilic substitution as well as the proton from the first position can also be substituted by other nucleophiles. The various routes followed according to their mechanistic approach to get access for both substituted and unsubstituted indenopyrazoles are:

(1) Cyclocondensation between hydrazine and similar derivative with carbonyl system.

(2) Using different starting materials.

2.1. Cyclocondensation between hydrazine and its derivative on 1, 3 difunctional system

This is a primary method used for the synthesis of substituted indenopyrazoles, wherein, the cyclocondensation reaction occurs between 1, 3-dicarbonyl compound or an α, β-unsaturated ketone with appropriate hydrazine which acts as a bidentate nucleophile. This methodology can be followed using various reactants such as:

2.1.1. Diketones

Cyclocondensation of 1,3-diketones with hydrazine results in polysubstituted indenopyrazoles, wherein this reaction is facile and rapid in nature. There are different methods used for such cyclocondensation reactions which are depicted in **Fig. 1**.

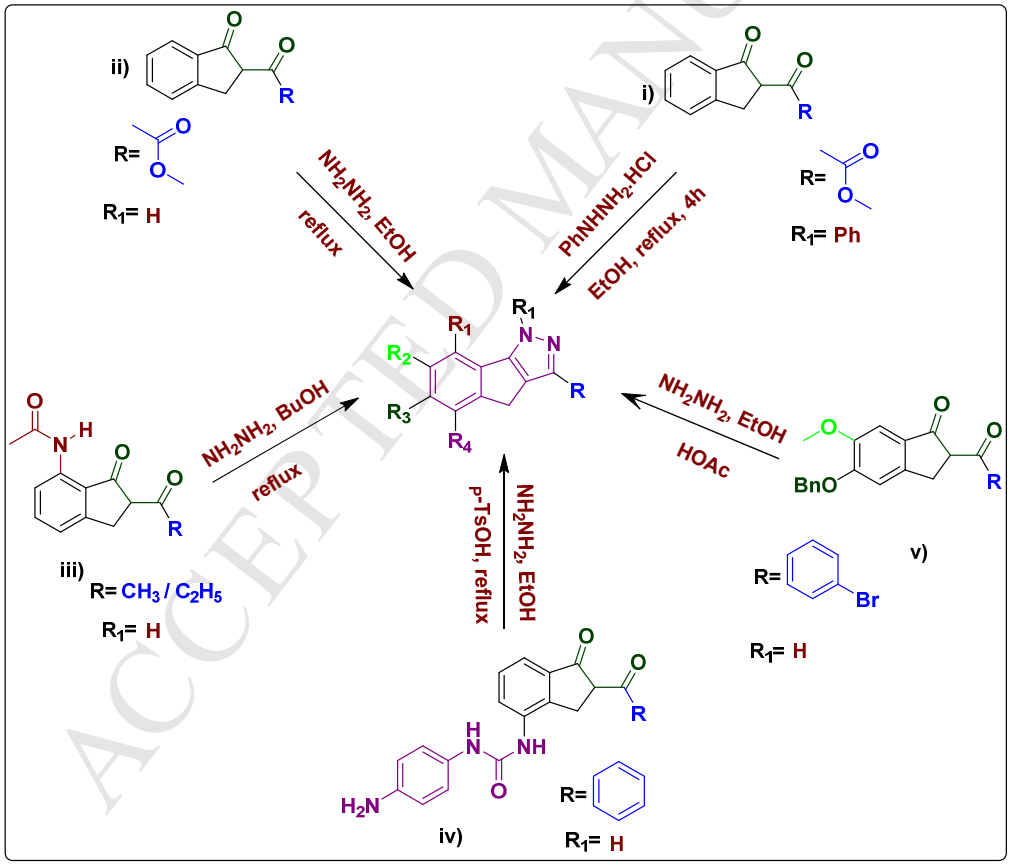


Fig. 1. Synthesis of indenopyrazoles using various diketones

Heghazi and coworkers [9] synthesized 1,4-dihydroindenopyrazole ester using 1,4-dihydroindenone diketoester and phenylhydrazine hydrochloride in ethanol (**Fig. 1**, **i**), while

indenopyrazoles with free NH were synthesized using hydrazine in ethanol [10, 11] (**Fig. 1**, **ii**). Further, indenopyrazoles were prepared using hydrazine in BuOH instead of EtOH which favored the increase in boiling point [12] (**Fig. 1, iii**). Similarly, *p*-toluenesulfonic acid (*p*-TsOH) in EtOH was used along with hydrazine and 4-substituted diketone which afforded indenopyrazole derivatives [13] (**Fig. 1, iv**), while Tao et al. [14] (**Fig. 1, v**) combined ethanol and acetic acid to obtain indenopyrazoles by cyclocondensation between hydrazine and diketone. However, in all the above cases, the use of hydrazine as a reactant in combination with ethanol as a solvent enabled an increase in the yield and consumed less time to complete the reaction.

2.1.2. α, β-unsaturated inden-1-ones

Indenopyrazoles were synthesized by simple condensation between α,β-unsaturated inden-1-one and hydrazine derivatives. Ahsan et al. [15] used substituted α,β-inden-1-one and substituted hydrazine in acetic acid to furnish indenopyrazole derivatives with 62% to 88% yield after recrystallization in absolute ethanol (**Fig. 2**, **i**). Rostom et al. [16] prepared indeno[1,2-c]-pyrazolines in good yields by simple condensation reaction between α,β-inden-1-one with 4-hydrazinobenzenesulfonamide hydrochloride in boiling ethanol (**Fig. 2**, **ii**). Inden-1-one was prepared using indenone which on subsequent Claisen condensation with different Het/Ar-aldehyde in presence of catalytic amount of bleaching earth (10 percent, pH 12.5) and PEG as green reaction solvent (green protocol) which resulted in various novel α, β-unsaturated indenopyrazoles with more than 90% yield in less time (**Fig. 2**, **iii**) [17]. However, indenopyrazoles were prepared with benzothiazole as substituent by stirring equimolar quantities of 2-arylidene-1H-indene-1,3(2H)-diones and hydrazinyl benzo thiazole/2-hydraziny-6-substituted benzothiazoles in dry pyridine/piperidine at room temperature for 3‑4 days gave low yields via regioselective synthesis. Further, several attempts were made to improve the yield by increasing the reaction temperature which ultimately intensified the resinification with no improvement in the yields (**Fig. 2**, **iv**) [18].

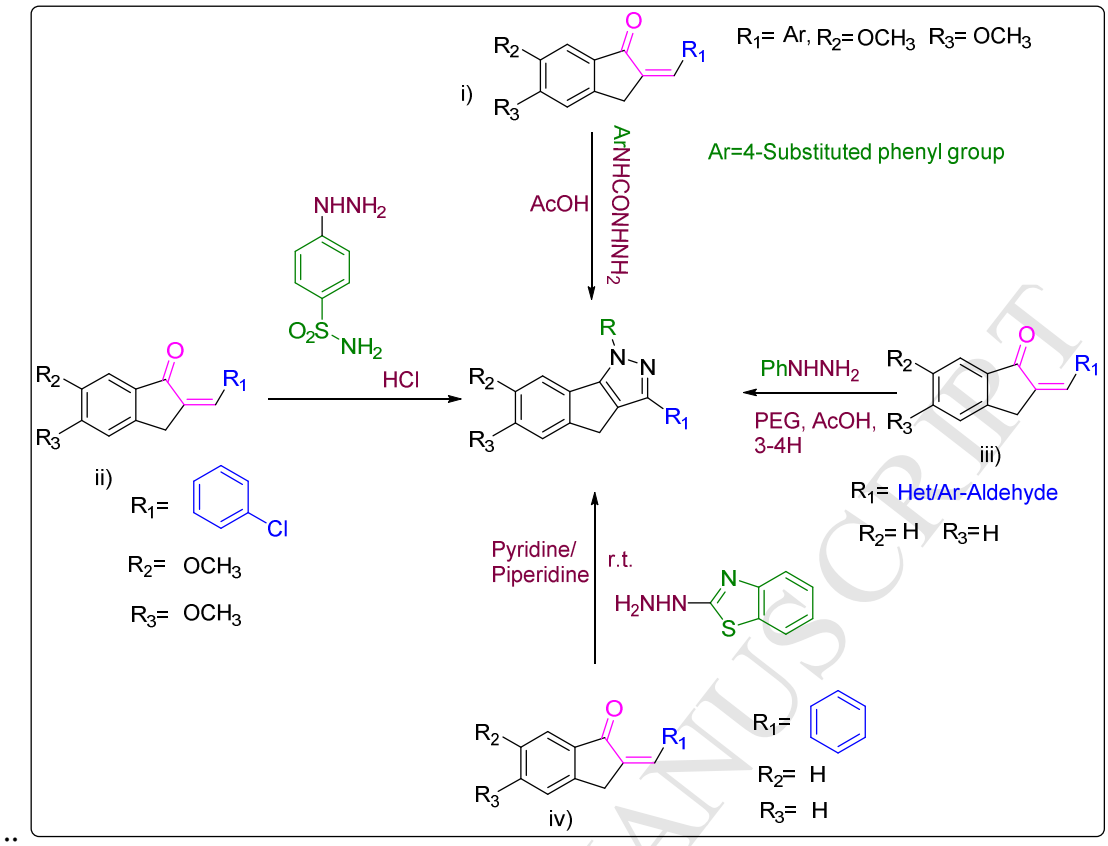


Fig. 2. Synthesis of indenopyrazoles from α, β-unsaturated inden-1-one

2.1.3. Cyclocondensation of thiodamide intermediate and hydrazine

In this type of cyclocondensation reaction, the intermediate formed was thioamide. Indenone reacted with different substituted isothiocyanates to afford the intermediate thioamide which on condensation with methylhydrazine resulted in the formation of different substituted indenopyrazoles with reasonable yields (54%) (**Fig. 3**, **i**) [19]. However, Minegishi et al. [20] used hydrazine hydrate to cyclize the thioamide with moderate yield (37−60%) (**Fig. 3**, **ii**).

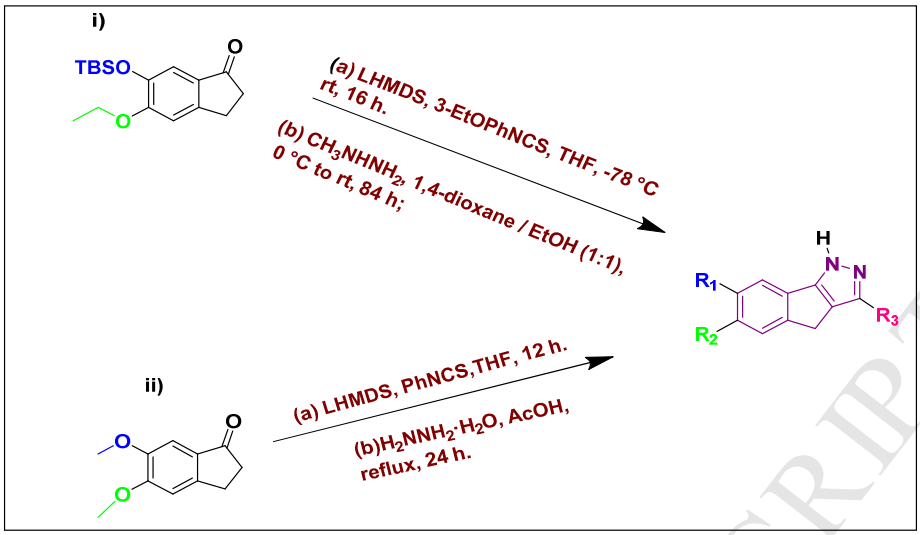
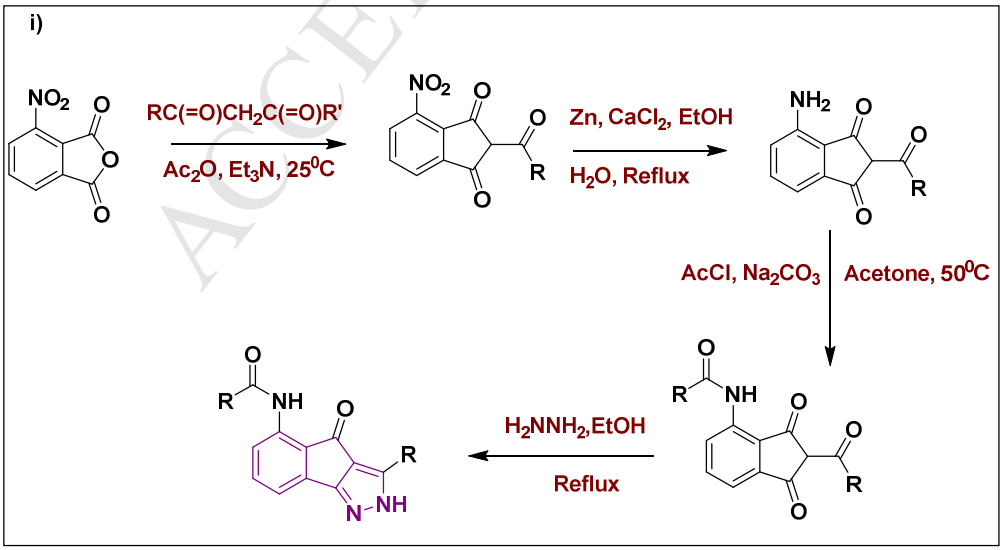


Fig. 3. Synthesis of indenopyrazoles by cyclocondensation of thiodamide intermediate and hydrazine

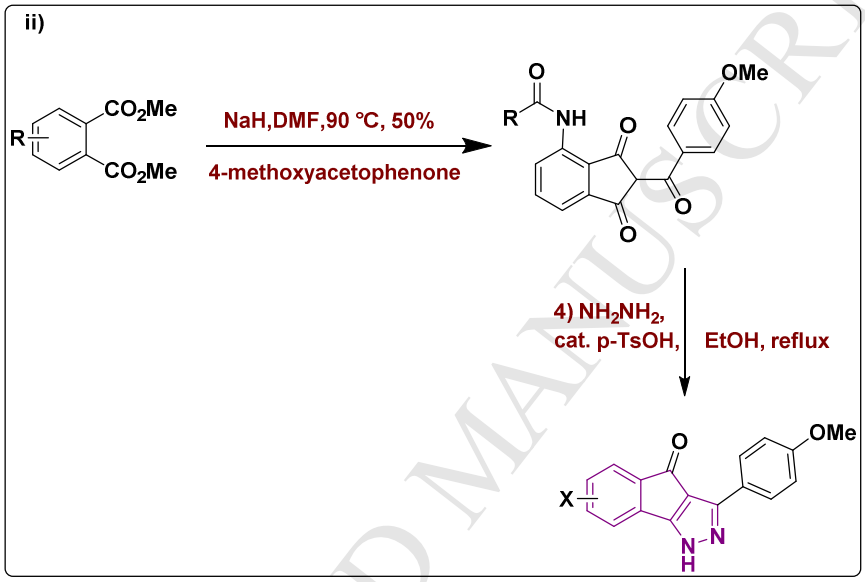
2.2. Using different starting materials

Eddy and coworkers [21] synthesized indenopyrazoles by initiating the reaction of 3-nitrophthalic anhydride with a properly substituted diketone which yielded a triketone (**Scheme 1**). This reaction was possible due to the merging of various heterocyclic groups only by changing the diketone (3, R = heterocycle), which on reduction followed by substitution with acylchloride afforded the formation of triketone amides. The formed triketone amides were further cyclized with hydrazine to yield indenopyrazoles along with an undesired 8-nitro regioisomer.



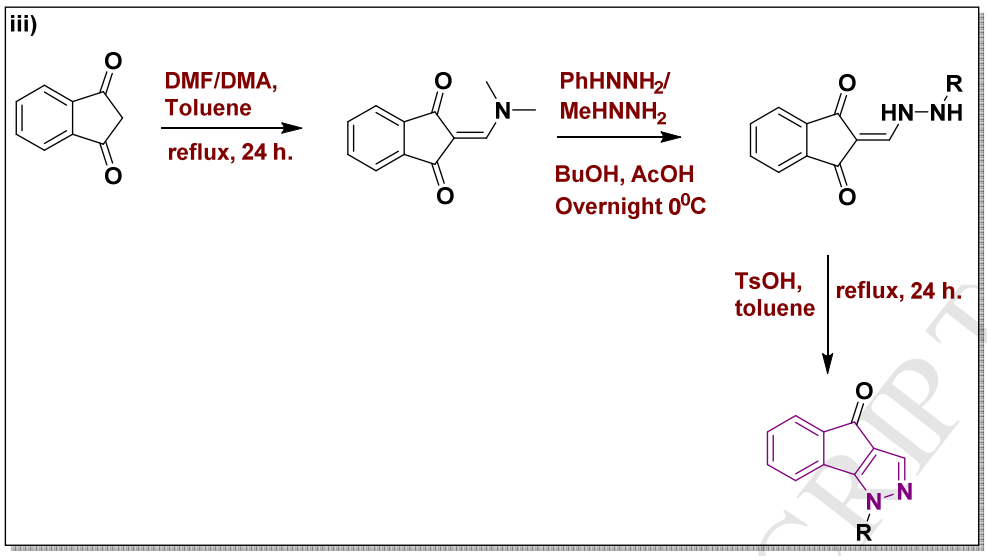
Scheme 1. Synthesis of indenopyrazoles using 3-nitrophthalic anhydride

Nugiel et al. [22] synthesized indenopyrazoles in two consequent steps with good yield (**Scheme 2**). In the first step, an appropriate phthalate ester was reacted with sodium hydride and 4-methoxyacetophenone at 90 °C in dimethylformamide (DMF), which afforded the desired tricarbonyl intermediate in good yield. Later, this triketone intermediate was reacted with hydrazine and a catalytic amount of *p*-TsOH by refluxing in ethanol for 2 h to afford the desired indenopyrazoles.



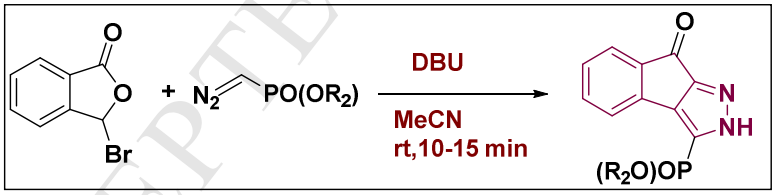
Scheme 2. Synthesis of indenopyrazoles from dimethyl 3-nitrophthalate

Furthermore, Angelone et al. [23] used dione as a starting material which reacted with DMF/DMA to obtain 2-(*N*,*N*-dimethylaminomethylene) indane-1,3-dione which was further reacted with methylhydrazine or phenylhydrazine in butanol and acetic acid as a catalyst to afford 2-(*N'*-methyl hydrazinomethylene)indane-1,3-dione and 2-(*N'*-phenyl hydrazinomethylene)indane-1,3-dione, respectively, which were cyclized to obtain 1-phenyl-1H-indeno[1,2-c]pyrazol-4-one (42% yield) and 1-methyl-1H-indeno[1,2-c]pyrazol-4-one (35% yield) by refluxing under acid catalyzed conditions in anhydrous toluene and in the presence of *p*-TsOH acid as a catalyst (**Scheme 3**).



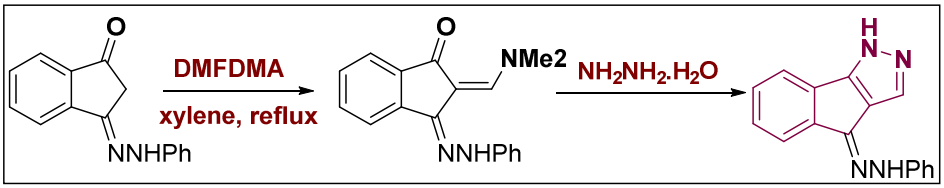
Scheme 3. Synthesis of indenopyrazoles from dione

Chaturvedi and coworkers [24] developed a new strategy for the synthesis of indenopyrazoles bearing a phosphonate group. This method followed a cascade reaction pattern of four consecutive reactions, namely addition-elimination, Seyferth−Gilbert homologation, transphosphorylation and 1,3-dipolar cycloaddition which afforded the formation of phosphoryl indenopyrazole scaffold (**Scheme 4**).



Scheme 4. Synthesis of indenopyrazoles from 3-bromoisobenzofuran-1(*3H*)-one

Elmaati [25] showed a simpler method for the synthesis of various heterocyclic compounds including substituted indenopyrazoles by using indane-1,3-dione derivatives, which on reaction with dimethylformamide dimethylacetal (DMFDMA) in refluxing xylene, yielded the enaminone followed by addition of hydrazine hydrate to yield various indenopyrazoles (**Scheme 5**).



Scheme 5. Synthesis of indenopyrazoles from (*E*)-3-(2-phenylhydrazono)-2,3-dihydro-1H-inden-1-one

3. Biological activities of indenopyrazoles

3.1. Antimycobacterial activity

Tuberculosis (TB) is one of the most frightening and debilitating disease caused by *Mycobacterium tuberculosis*, which has infected more than one third of the global population [26]. According to WHO, 9.4 million people around the globe and among which 1.6-2.4 million cases were reported in India. It was estimated that around 1.7 million people died with these dreadful disease in 2009 [27]. Nowadays, many patients have developed multi-drug resistance against the currently available anti-tubercular drugs which is a biggest challenge and this has resulted around 1.3 million drug resistant cases during the years 2010-2015. In India, currently the first line treatment regimen uses a combination of various TB drugs such as Isoniazid, Rifampicin, Pyrazinamide and Ethambutol which is coupled with severe side effects including rashes, fever, neuropathy, hepatotoxicity, ocular toxicity, thrombocytopenia and drug induced hepatitis. These side effects warrants the need to identify more effective antimycobacterial agents with minimum side effects.

Considering these facts, a diverse array of heterocyclic moieties were synthesized as anti-tubercular compounds. Ahsan and coworkers [15] synthesized a series of indenopyrazole based compounds exhibiting inhibitory potential against *Mycobacterium tuberculosis* H_{37}RV and multi-drug resistant *M. tuberculosis* (MDR-TB). The compound 3-(4-fluorophenyl)-N-(4-chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3h-indeno[1,2-c]pyrazole-2-carboxamide (**4a**) (**Fig. 4**) exhibited greater potency with MIC values of 0.83 and 3.32 µM against *M. tuberculosis* H_{37}RV and MDR-TB strains, respectively. Similarly, *N*,3-bis(4-fluorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide (**4b**) **(Fig. 4)** was synthesized which showed to be most promising exhibiting MIC value of 0.78 µM against *M. tuberculosis* HRV and MDR-TB strains [28]. The SAR studies indicated that 3-substituted

compounds with electron withdrawing groups such as 4-flourophenyl and 4-pyridyl exhibited more potency followed by 2-chlorophenyl, while the electron donating groups such as 4-methoxyphenyl and 3,4-dimethoxyphenyl were found to be less potent.

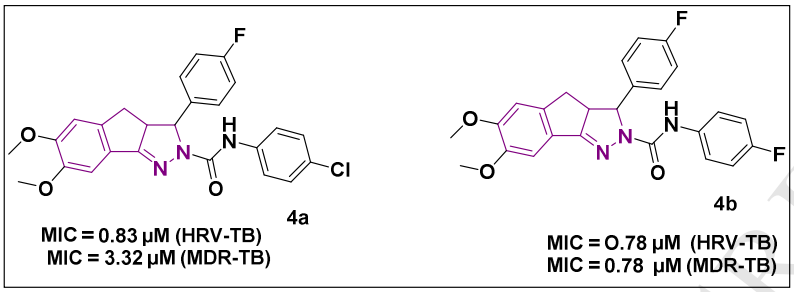


Fig. 4. Indenopyrazoles exhibiting antimycobacterial activity

3.2. Anti-psychotic activity

Schizophrenia is a chronic and neuropsychiatric disorder affecting around 1% of the world's population [29]. This disease is categorized based on its core symptoms: (i) negative symptoms (alogia, affective flattening, anhedonia, avolition and apathy), (ii) positive symptoms (delusions, hallucinations and thought disorder), and (iii) cognitive impairment [30]. Typical antipsychotic drugs [aripiprazole, haloperidol (Haldol), perphenazine (Trilafon)] currently available in the market have been used for the treatment of schizophrenia [31-33], which have ample side effects like extrapyramidal side effects (EPS) that can be either acute (Parkinsonism, akathisia, dystonia) or of later onset (tardive dyskinesia), weight gain, glucose and lipid abnormalities [34]. Therefore, to avoid such side effects, there is a need to discover new, safer and potent antipsychotic medications which is tremendously important. From the clinical perspective to develop a new antipsychotic drug, Lemke and coworkers [8] reported a series of indenopyrazoles as antidepressants. From the entire series, 2-ethyl-3-methyl-4-(l-methyl-4-piperidyl)-4-hydroxyindeno[1,2-c]pyrazole **5a** (**Fig. 5**) was identified which showed considerable depression of spontaneous motor activity in mice at all the tested doses and the safety index (LD_{50}/ED_{50}) was 17.6 which was remarkably higher than others. Moreover, Love et al. [35] patented 3-substituted pyrazoloindenone azines **5b** (**Fig. 5**) which showed anti-depressant and other CNS related activities.

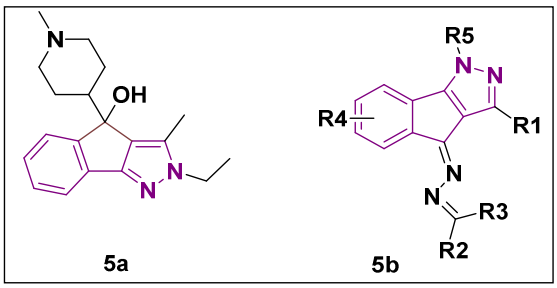


Fig. 5. Indenopyrazoles exhibiting anti-psychotic activities

3.3. Antimicrobial activity

An agent that kills microorganisms or inhibits their growth is termed as an antimicrobial agent. Bacterial and fungal infections are the most common causes of death in immunocompromised patients [36,37]. The rising incidence of multidrug resistance to microbial infections has become a major global health problem [38]. To address this global problem, there is a continuous need for the development of highly potential antimicrobial drugs with lower toxicity. To achieve this objective, Ahsan et al. [39] performed detailed analysis based on pharmacophore identification, toxicity prediction, lipophilicity and bioactivity on 3,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide/carbothioamide analogues by adopting an *in silico* strategy such as Petra, Orisis, Molinspiration and ALOGPS (POMA). Among them, 3-(4-fluorophenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carbothioamide **6a** (**Fig. 6**) was predicted to be the most efficient compound as compared to the standard ciprofloxacin with MIC value of 4 µg/ml against various tested bacterial strains, while 3-(4-methoxyphenyl)-6,7-dimethoxy-3,4-dihydro-3H-indeno[1,2-c]pyrazole-2-carboxamide **6b** (**Fig. 6**) was found to be less active as compared to the standard fluconazole, but emerged as the most active compound with MIC values of 2-4 µg/ml against various tested fungal strains. Therefore, based on the results, SAR studies showed that compound having 3-aryl group with 4-fluorophenyl, 3,4-dimethoxyphenyl, 4-pyridinyl, 4-methoxyphenyl and phenyl group as substitutions showed good to moderate activity. More and coworkers [40] designed and synthesized a series of 3-aryl-1-heteroaryl indeno[1,2-c]pyrazol-4(1H)-ones and were evaluated as potential antimicrobial agents by inhibiting Gram-positive, Gram-negative as well as a fungal strain. Among them, compound **6c** (**Fig. 6**) (MIC value of 0.0036 µmol/ml) was found to be more potent than fluconazole (MIC value of 0.0050 µmol/ml) against *A. niger*. Similarly, a series of 3-alkyl indeno[1,2-c]pyrazoles possessing 4-substituted thiazole moiety at position-1 were

synthesized and their antimicrobial activity were screened against various bacterial strains as well as a fungal strain. Among the tested series, most of the compounds showed good to moderate *pMIC (-log MIC) values against *E. coli*, but the analogue substituted with 4-chlorophenyl pharmacophore at C4 [**6d**, **6e**, **6g**, **6f** (**Fig. 6**)] of the thiazole moiety exhibited very high activity [41]. However, Acharya and coworkers [17] synthesized a series of compounds (**Fig. 6**) containing indenopyrazole as a core moiety and evaluated their antibacterial as well as antifungal activities. Among the series, different analogues such as **6h**, **6i**, **6j** and **6k** showed good antibacterial activity against various bacterial strains such as *E. coli*, *S. aureus*, *P. vulgaris* and *B. subtilis.* While, the compounds **6l**, **6h**, **6j** and **6k** (**Fig. 6**) exhibited significant antifungal activity against various fungal strains such as *A. niger*, *A. flavus* and *P. chrysogenum.* The SAR studies revealed that the activity increased due to the presence of -OH, -Cl or -NO_2 groups present on the pyrazole substituted aryl ring of indenopyrazole.

3.4. Anti-hypertensive activity

Hypertension is a chronic medical condition and it is predicted that around 1.56 billion people will be affected worldwide by the year 2025 [42]. Amongst the drugs used for the cardiovascular disease, β-blockers are an essential class of drugs, applied against hypertension, heart attack, angina pectoris and certain arrhythmias [43]. A number of β-blockers are available, for e.g. Sectral (acebutolol), Tenormin (atenolol), Kerlone (betaxolol); however, they have few side effects like bronchoconstriction action on the bronchial smooth muscle, β3 receptor stimulation, block and alteration of lipase enzyme activity which interfere with triglyceride synthesis [44, 45]. For these reasons, it is necessary to identify new β-blockers which are free from side effects. Angelone et al. [23] synthesized substituted (Z/E)-indeno[1,2-c]pyrazol-4(1H)-one oximes and reported their β-blocker cardiac activity. Among the tested compounds, **7a** (**Fig. 7**) proved to be the most promising analogue which exhibited β-blocker function with greater potency and effectiveness, while counteracting β1-adrenergic stimulation. Whereas, compound **7b** (**Fig. 7**) having n-butyl group on the aminic portion showed positive inotropism suggesting that this molecule as a partial β-adrenergic agonist rather than antagonist. However aminic portion having iso-propyl substituent on the nitrogen atom was less potent.

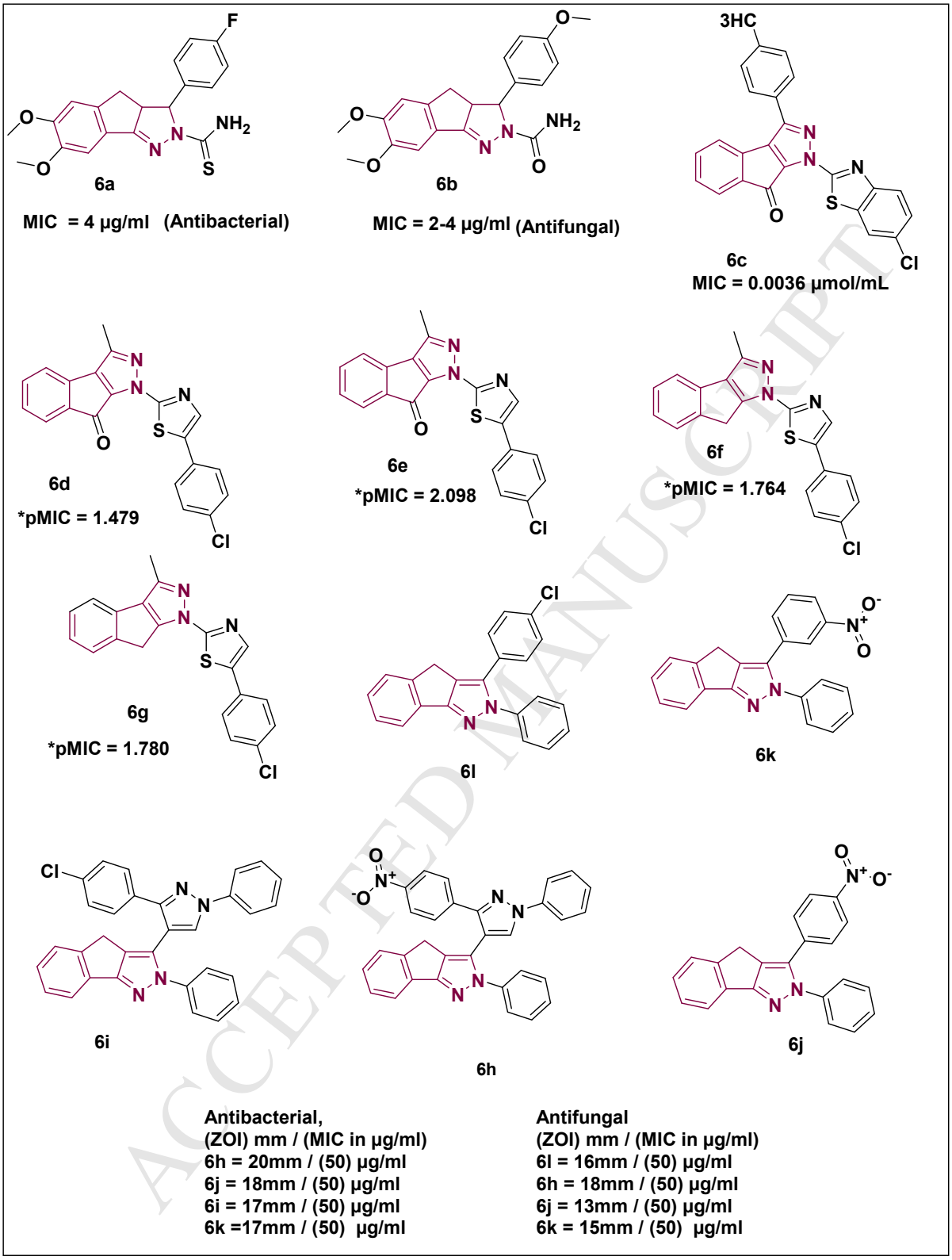


Fig. 6. Various indenopyrazoles exhibiting antimicrobial activities

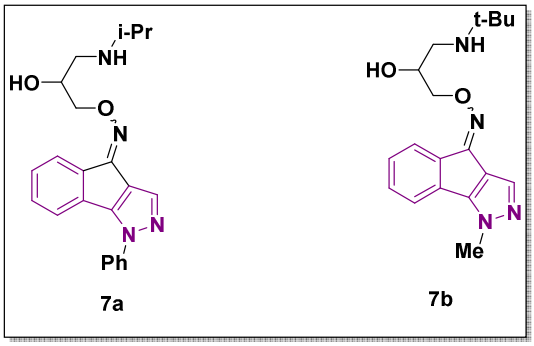


Fig. 7. Indenopyrazoles exhibiting antihypertensive activities

3.5. Cannabinoid receptor affinity

Cannabinoid receptors such as CB2 and CB1 belong to the rhodospin-like family of G-protein-coupled receptors (GPCRs), which control different multiple intracellular signal transduction pathways [46]. CB2 receptor expressed in eosinophils and natural killer and B-lymphocytes and also in peripheral tissue (tonsils, thymus, spleen, pancreas), peripheral nerve terminals, skin tumor cells, and it was also expressed abundantly in various types of inflammatory cells and immune competent cells altering the maturation of macrophages which specifically mediate both immunosuppressive and immunostimulatory effects [47-50]. The multifocal expression of CB2 immunoreactivity suggests reassessment of the possible roles played in CNS by this receptor subtype; however, the presence of ligands can interact selectively with CB2 receptors which could be higher than cannabinoid receptor subtype involving known pathophysiological processes, i.e. peripheral antinociception, immunomodulation, inflammation, neurodegeneration, uncontrolled cell proliferation [51,52]. Therefore, individuation of new classes of CB2 active and selective ligands have gained a renewed interest. From the viewpoint to synthesize different classes of synthetic compounds having CB2 affinity and selectivity, the pyrazole possessing derivatives were demonstrated through various studies [53]. In order to extend the application of indenopyrazoles, Murineddu et al. [54] prepared new 1,4-dihydroindeno[1,2-*c*]pyrazole-based ligands with CB2 affinity (**Fig. 8**). Among the series, analogue (**8c**) showed single digit nanomolar affinity for cannabinoid CB2 receptors and the compound **8d**, as well as **8a**, **8b** were considered as leads which exhibited agonist activity toward CB2 receptors in an *in vitro* model based on human promyelocytic leukemia (HL-60) cells. Furthermore, the SAR study exposed that the simultaneous introduction of two substituents (CH_3 and Cl) at positions 6

and 7 of the indenopyrazole core gave rise to compounds that retained good to moderate activity; however, fluoro, methyl, and methoxyl derivatives maintained a moderate CB2 affinity.

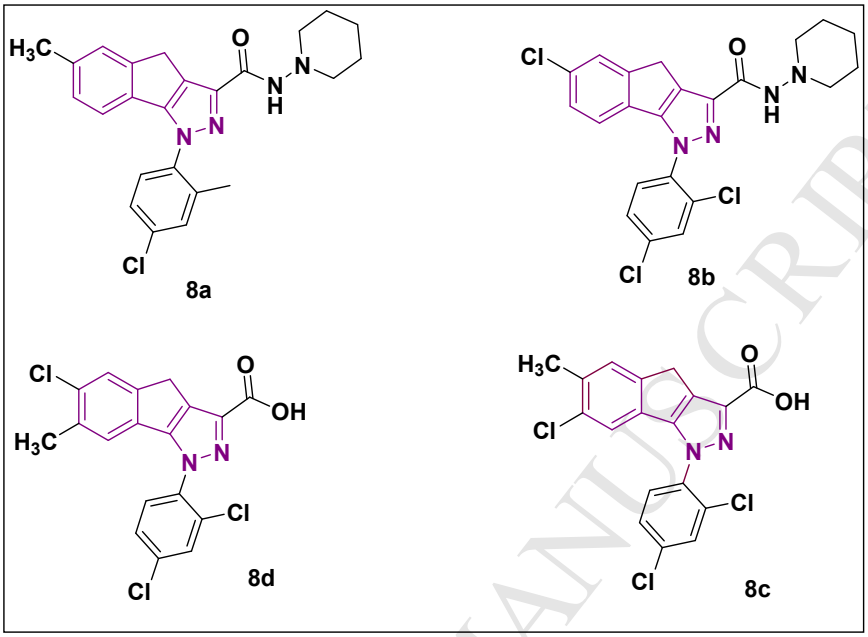


Fig. 8. Various indenopyrazoles exhibiting cannabinoid receptor affinity

3.6. Anticancer activity

Cancer is a broad group of disease, described as uncontrolled cell proliferation and spread of aberrant cells from their site of origin [55]. It is considered as one of the most lethal disease and is reported to be the second most common cause of death after cardiovascular disease [56]. Despite the availability of huge number of chemotherapeutics and effective solutions to address the problem of cancer, there has been an increasing number of cancer related deaths which has become a serious threat to human health. Hence, to overcome these problems, there has been a greater attention by researchers across the globe to develop and identify effective anticancer therapeutics [57]. Consequently, indenopyrazoles which exhibited broad spectrum of target based anticancer activities were developed by various researchers which included:

3.6.1. Tubulin polymerization inhibitors

Microtubules are very important cytoskeletal components concerned with the regulation of cell architecture, since they play an important role in cell division, differentiation and cell maintenance [58]. Therefore, the inhibition of microtubule function using tubulin targeting agents is one of the validated approach in anticancer therapy. However, the existing anti-tubulin agents faced many problems in clinical use including poor bioavailability, poor water solubility, toxicity and multi-drug-resistance (MDR) [59-62]. To overcome these limitations, it was crucial to develop small molecules with no such limitations and efficient enough to treat MDR tumors as well as inhibit tubulin polymerization [63]. Minegishi et al. [20] designed a series of methyl 3-((6-methoxy-1,4-dihydroindeno[1,2-c]pyrazol-3-yl)amino)-benzoate analogues in which analogue **9a** (GN39482) (**Fig. 9**) was identified as a promising lead with IC_{50} value of 2.47 nM on HeLa cell line and also inhibited tubulin polymerization. The SAR study based on the structure of indenopyrazole showed that both methoxy group at R1 position and a methoxy carbonyl group at R2 position of the anilinoquinazoline framework were essential for the maximum cell growth inhibition. Similarly, a series of 7-substituted 1-methyl-1,4-dihydroindeno[1,2-c]pyrazoles were designed, synthesized and evaluated for anticancer activity by Liu et al. [19], wherein they found that compounds **9b** and **9c** showed promising activity against HepG2, PC3, HeLa and MCF-7 cancer cell lines at a nano molar range and the mechanistic study showed inhibition of tubulin polymerization. While the SAR study of **9b** and **9c** showed that acetamide and N-hydroxyacetamide substitution on **9b** and **9c** enhanced the potency. In addition, 1,4-dihydroindenopyrazole-linked oxindoles were synthesized and evaluated for anticancer activity. Among the tested derivatives, compounds **9d** and **9e** (**Fig. 9**) showed excellent anti-proliferative effect with IC_{50} values ranging from 1.33-2.16 µM on HeLa cell line. The SAR study of compounds **9d** and **9e** suggested that dimethoxy substitution on indenopyrazole ring and 6-Cl substitution followed by methoxy substitution on oxindole ring exhibited promising cytotoxicity. Furthermore, the mechanistic studies revealed that the lead molecules exhibited disruption of microtubule network and induced p53-dependant apoptosis [64].

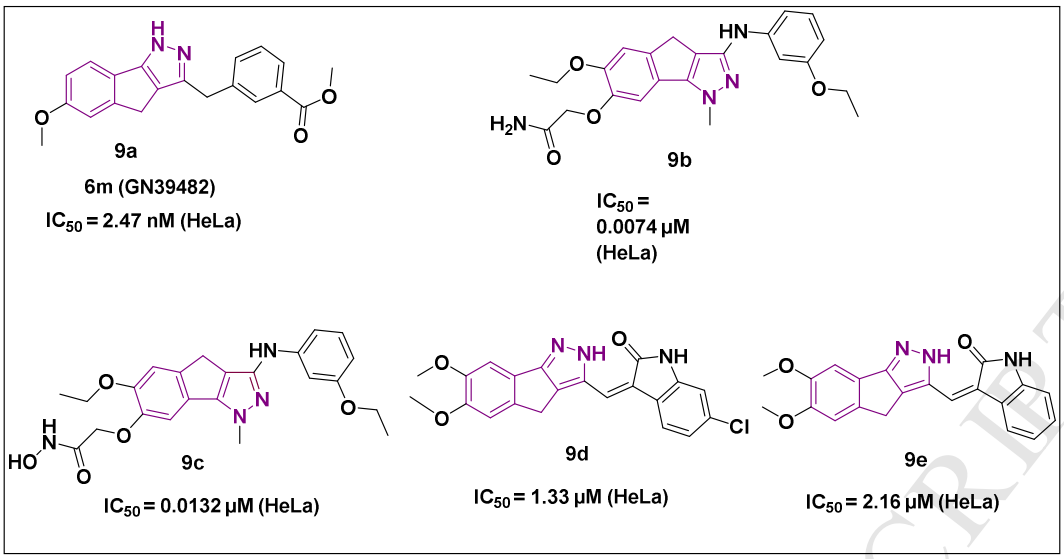


Fig. 9. Diverse indenopyrazoles exhibiting tubulin polymerization inhibition activity

3.6.2. Cyclin-dependant kinase inhibitors

Cyclin dependant kinases (CDKs) are characterized as key components for the cell cycle regulatory machinery like cell division cycle, transcription, apoptosis and differentiation [65]. The evidence of link between CDK related malfunctions and tumor growth had forced researchers globally to undertake an intensive search for small molecules with CDK inhibitory activity as an approach to anticancer chemotherapy [66, 67]. In this regard, Nugiel and co-workers [68] showed that indenopyrazole-linked semicarbazides can function as cyclin-dependent kinase (CDK) inhibitors. Among the tested derivatives, compound **10b** (**Fig. 10**) exhibited potency against CDK2 and CDK4. Furthermore, amino indenopyrazole scaffold substituted with different small aliphatic groups also exhibited CDK inhibitory activity [21]. The compound **10a** (**Fig. 10**) showed more activity against CDK2 as compared to CDK4. Later, Yue and coworkers [21] synthesized and evaluated the effects of substitution of alkyls, heterocycles and substituted phenyl moieties at the C3 position of the indeno[1,2-c]pyrazol-4-one scaffold as CDK inhibitors. It was observed that the substitution of heterocyclic moiety at the C3 position (in case of compound **10c**) (**Fig. 10**) exhibited promising CDK inhibitory activity as compared to other substitutions. In addition, it was noticed that substitutions at C3 position with a heterocyclic moiety and C5 position with a semicarbazide moiety were found to exhibit CDK enzyme inhibitory activity in nanomolar range. While the substitution with only primary and secondary amide showed similar or better CDK4/D1 and CDK2/E inhibition as compared to the parent ester. Whereas, in case of

cyclic amide substitution only seven membered ring (compound **10d**, **Fig. 10**) exhibited enhanced binding affinity for CDK4/D1 which was 10 fold more selective than CDK2/E [10]. In order to extend the potential of indenopyrzole derivatives as CDK inhibitors, in *silico* studies (3D-QSAR, CoMFA) were performed [69] and these studies confirmed a strong correlative and predictive capability with a cross validated correlation coefficient of 0.747 and 0.755 for CDK4 and CDK2 inhibition, respectively. The conventional and predictive correlation coefficients were estimated to be 0.913 and 0.760 for CDK4, 0.941 and 0.765 for CDK2, respectively.

On the other hand, Shahlaei and coworkers [70] performed computational studies including docking through modeling ligand interaction and MIA-QSAR analysis to evaluate the bioactivity of 54 anticipated indenopyrazoles as novel CDK2 antagonists. ADME-Tox evaluation was also performed and two indenopyrazole derivatives, **10e** and **10f** (**Fig. 10**) were identified as promising CDK2 antagonists.

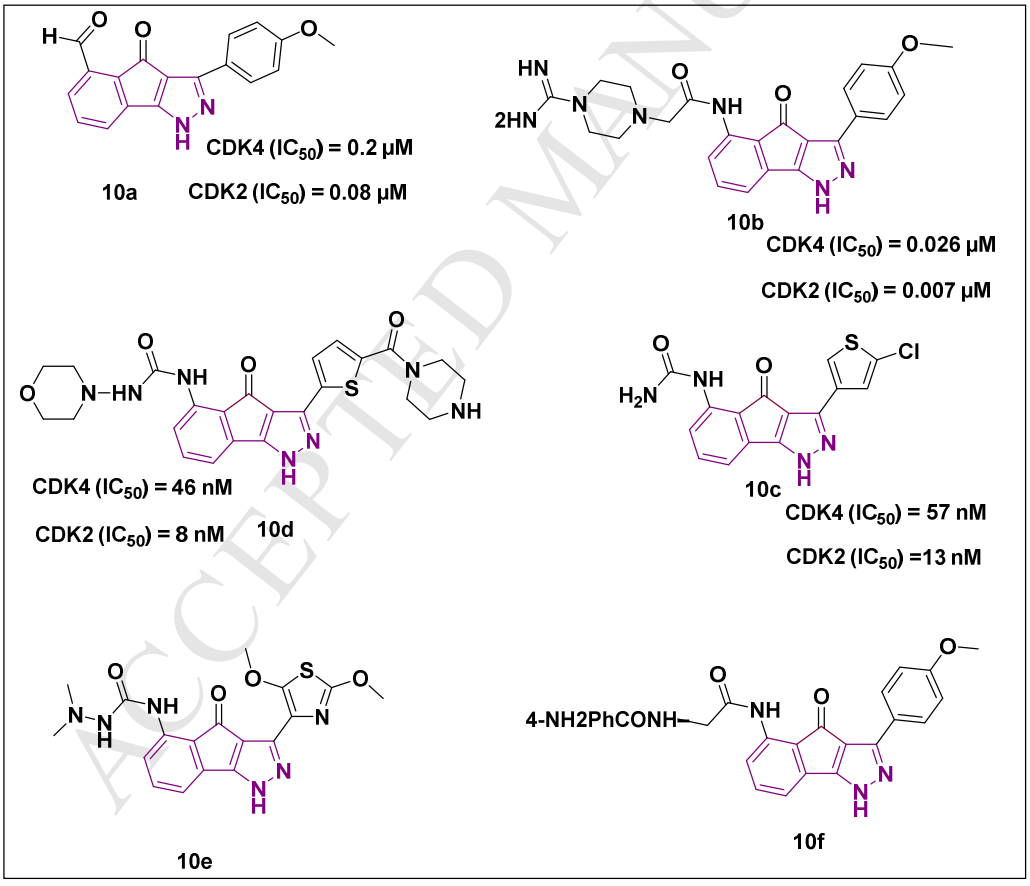


Fig. 10. Various indenopyrazoles exhibiting cyclin-dependant kinase inhibitor activities

3.6.3. Tyrosine kinase inhibitors (EGFR and VEGFR-2)

Protein tyrosine kinase inhibitors emerged as therapeutic tools for the treatment of various diseases including cancer [71, 72]. Among the protein tyrosine kinases, EGFR (epidermal growth factor receptor) was established as an authenticated target for the development of new anticancer agents, since it is a key mediator in cell signaling related to proliferation, cell growth, survival and migration [73-75]. Moreover, EGFR also played a critical role in the development of non-small cell lung cancer (NSCLC) as well as breast cancer [76]. Overexpression of EGFR in many solid cancers was linked with poor prognosis [77]. Considering these factors, it was warranted to develop a new anticancer hybrid which inhibited EGFR and this was observed as a significant approach. The vascular endothelial growth factor and its tyrosine kinase receptor (VEGFR-1 and VEGFR-2) played a significant role in angiogenesis [78, 79], which helps in the progression of metastasis and growth of most solid tumors [80]. Therefore, VEGFR was identified as a validated target for the cancer chemotherapeutic approach [81].

In order to expand the effective anticancer therapy, development of heterocyclic small molecules with tyrosine kinase inhibition potency is a leading strategy followed by various medicinal chemists. A number of indenopyrazoles-substituted at 3' or 4' position with basic side chains like (4-methylpiperazin-1-yl)methyl were synthesized and these compounds showed KDR kinase inhibition activity (VEGFR2 kinase insert domain-containing receptor tyrosine kinase). Among the tested series, compound **11a** (**Fig. 11**) showed an acceptable selectivity profile, along with good efficacy in primary *in vivo* model in whole cells (KDR activity: IC_{50} value = 0.18 μM) against VRGFR-2 was identified by high-throughput screening [82]. Recently, Khan and coworkers [83] prepared a series of indenopyrazole chalcones and evaluated their cytotoxic potential against A549 (human liver cancer cell) as EGFR/Akt pathway inhibitors. Amongst the series, the analogues (**11b**, **11c**, **11d**) showed promising IC_{50} values in the range of 3.53-5.21 μM as compared to Erlotinib (standard) with IC_{50} value of 10.26 μM. The SAR study revealed that increase in substitution of electron donating group (-OCH_3) on last benzene ring enhanced the activity as compared to methoxy substitution on indenopyrazole ring.

Usui and coworkers [13] performed *in silico* screening of 400,000 compound libraries for tyrosine kinase inhibitory activities and they found that indenopyrazole scaffold was one of the most frequently used privileged structure among the top 100 scored compounds. Based on this *in silico* screening, indenopyrazole derivatives were designed and synthesized and evaluated for EGFR tyrosine kinase inhibitory activity. The biological evaluation on the tested series revealed that compounds **11e** and **11f** (**Fig. 11**) showed significant inhibition of

A431 cell growth (GI_{50} values = 0.062 and 0.057 μM, respectively), while the analogue **11b** exhibited both EGFR and VEGFR-2 (KDR) inhibitory activities, whereas the analogue **11c** showed complete inhibition of only VEGFR-2 tyrosine kinase. The SAR study on analogue **11b** and **11c** showed that amino and hydroxy substitution on carboxamide moiety were found to be more potent.

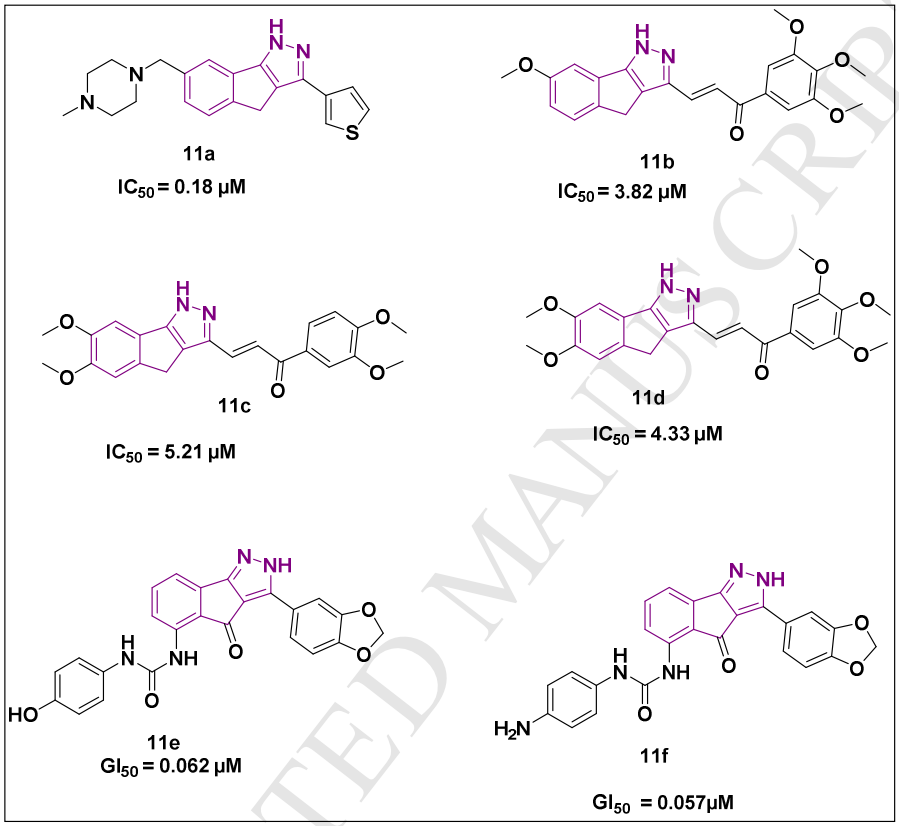


Fig. 11. Various indenopyrazoles exhibiting tyrosine kinase inhibitor (EGFR AND VEGFR-2) activities

3.6.4. Checkpoint kinase-1 inhibitors (CHK-1)

CHK-1 coordinates in the DNA damage response (DDR) which maintains the genome integrity through an integrated activity of multiple pathways [84], while CHK-1 helps in the initiation of cell cycle checkpoints such as cell cycle arrest, DNA repair and cell death to prevent damaged cells from progressing through the cell cycle [85]. Therefore, CHK1 inhibitors were identified as a chemopotentiating strategy to control cancer. To address these issues, small molecules with CHK-1 inhibition potency were developed. Tong and coworkers [86] identified a new molecule bearing a 1,4-dihydroindeno[1,2-c]pyrazole core **12a** (IC_{50}

value = 510 nM) as a new class of checkpoint kinase (CHK-1) inhibitors, based on high throughput screening. Further, screening of other compounds showed that replacement of the fluoro moiety from compound **12a** (**Fig. 12**) with carboxylic group (compound **12b**, **Fig. 12**) exhibited promising results (IC_{50} value = 20 nM) with a 25-fold more potency as compared to compound **12a**. Further studies by the same group [87] with regard to the effects of substitution at four open positions on the phenyl ring of the 1,4-dihydroindeno[1,2-c]pyrazole revealed that *bis*-substitution at 6- and 7-positions exhibited more potent CHK-1 inhibitory activity as compared to other *bis*-substitutions. While, compound **12c** (**Fig. 12**) with (trans-4-hydroxy-cyclohexylamino)-carbonyl substituted at the 7-position and 6-position bearing methoxyl groups were identified as the most suitable substituents.

Later, Tao and coworkers [88] described an extensive structure-activity relationship and compounds with substitutions at the 3-position of indenopyrazole ring were found to be promising CHK1 inhibitors. Amongst the tested series, compounds **12d** and **12e** (**Fig. 12)** emerged as promising lead molecules which exhibited retention of its cell-based assay and enzymatic inhibition as compared to its original lead compound. Moreover, the identified leads exhibited some favorable physiochemical properties like lower molecular weight, lower ClogP values, and the absence of the hydroxyl group.

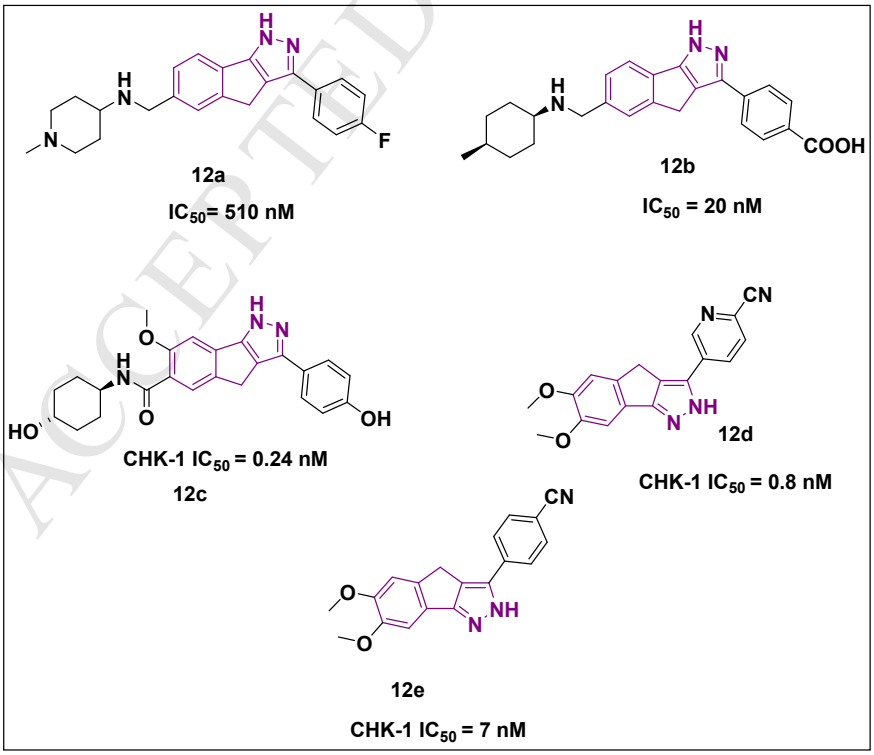


Fig. 12. Diverse indenopyrazoles exhibiting checkpoint kinase-1 inhibitors (CHK-1) activities

3.6.5. Hypoxia-inducible factor 1 inhibitors

HIF-1 is a transcription factor responsible for activation of multiple genes which regulate a number of vital processes required for the adaptation and progression of a cancer cell. Therefore, the inhibition of HIF-1 is considered as a validated approach for the development of cancer therapeutics [89]. Minegishi et al. [90] synthesized a series of 3-aniline substituted indenopyrazoles as a new class of HIF-1α inhibitors. SAR studies revealed that indenopyrazole ring with no substitution and the presence of cyclic ether skeleton on the aniline ring dramatically enhanced the potency. Among the ether substitutions on the aniline ring, 3,4-ethylenedioxyaniline derivative **13a** (**Fig. 13**) was found to be the most potent derivative (IC_{50} value = 0.014 μM), while the methylene-dioxyaniline substituted analogue **13b** (**Fig. 13**) inhibited the HIF-1 transcriptional activity with an IC_{50} value of 0.27 μM.

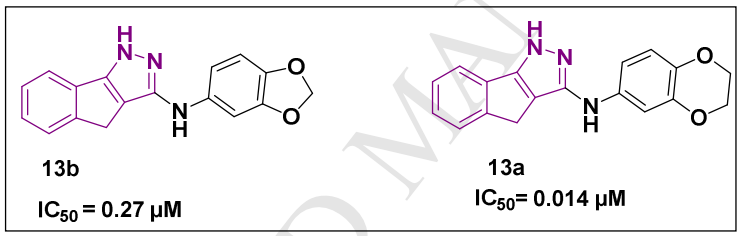


Fig. 13. Indenopyrazoles exhibiting hypoxia-inducible factor 1 inhibitory activities

4. Conclusions

Literature survey suggests that indenopyrazole is a privileged scaffold in medicinal chemistry exhibiting diverse pharmacological activities. In this review, diverse strategies employed for the synthesis of an array of substituted indenopyrazoles through various reactions were discussed at length. Moreover, these synthetic protocols assists pharmaceutical chemists to generate a library of indenopyrazoles based on high throughput screening (HTS) approaches. Furthermore, the pharmacological importance of indenopyrazoles have been comprehensively studied for different biological activities such as anti-mycobacterial, antipsychotic, antihypertensive, cannabinoid receptor affinity, antimicrobial, etc. From the perspective, to develop an anticancer therapy having broad spectrum target based anticancer activity, diverse indenopyrazoles which functioned as inhibitors which include cyclin-

dependant kinase inhibitor (CDK), checkpoint-1 kinase inhibitor (CHK-1), tyrosine kinase (EGFR, VEGFR) inhibitors, hypoxia-inducible factor-1 inhibitors, etc. were investigated by various researchers. However, still there is an ample unsolved mystery around this privileged scaffold and further investigations on this scaffold may result in the identification of different newer molecular targets, which can generate more promising and encouraging results for diverse medical applications. In addition, this overview would help in the further progression to identify novel synthetic strategies for generating efficient molecules with enhanced bioactivity, improved specificity and lower toxicity.

Acknowledgments

Authors would like to acknowledge UGC, New Delhi for the award of research fellowship. Authors would also like to thank CSIR, Government of India for financial support under the 12th Five Year plan project "Affordable Cancer Therapeutics" (CSC0301). (*Manuscript Communication No. IICT/Pubs./2018/366*)

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Highlights

- Synthetic strategies of various substituted indenopyrazoles are discussed.
- Diverse biological functions of substituted indenopyrazoles are outlined.
- Indenopyrazoles as target-based inhibitors for anticancer activity are described