Synthesis and Characterization of Isoindolinone derivatives as potential CNS active agents

Project Report-1
Masters of Sciences

In

Chemistry (Hons.)

By

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Registration No. 11615943

Under the guidance

Of

Dr. Gurpinder Singh

Department of Chemistry

Lovely Professional University, Punjab, India

DECLARATION

I hereby affirm that the dissertation entitled "Synthesis and Characterization of Isoindolinone derivatives as potential CNS active agents" submitted for the award of Master of Science in Chemistry and submitted to the Lovely Professional University is the original and authentic study that I have carried out from August 2017 to November 2017 under the supervision of Dr. Gurpinder Singh. It does not contain any unauthorized works of other scholars, those referred are properly cited.

Name and Signature of the Student
Kritika Chopra
Reg. No.: 11615943

Certificate

This is to certify that the pre-dissertation project entitled **"Synthesis and Characterization of Isoindolinone derivatives as potential CNS active agents**" submitted by **Kritika Chopra** to the Lovely Professional University, Punjab, India is a documentation of genuine literature review of coming research work approved under my guidance and is commendable of consideration for the honour of the degree of Master of Science in Chemistry of the University.

_____

Supervisor
Dr. Gurpinder Singh
Assistant Professor

Acknowledgement

This project report is the result of half of year of work whereby I have been accompanied and supported by many people. It is a pleasant aspect for me to express my gratitude for them all.

I would like to thank my supervisor **Dr. Gurpinder Singh**, Department of Chemistry, Lovely Professional University. Madam guided me when ever, where ever it was needed. Madam motivated me with his positive thoughts and positive attitude. I became punctual and dedicated to my work it is the result of his hard work. She shared her experience and made me to overcome all those obstacles which were present there.

I would like to thank also **Dr. Ramesh Chand Thakur (HOD),** Department of chemistry. He provided us with all the basic amenities which we required in this project. We were provided with a calm and stable environment which helped us to maintain our performance.

I do want to say thanks lab assistant for providing his support whenever it was required. My word of acknowledgement can never express the sense of regard towards all those personalities who have brought me to this position in my life.

Last but not at the least important, I owe more than thanks to my family, for their support and unconditional love and care that they have always showered upon me. I owe my each and every success to them.

Regards:

Kritika Chopra

11615943

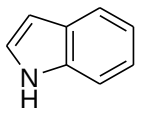
M.Sc. Chemistry Hons.

INTRODUCTION

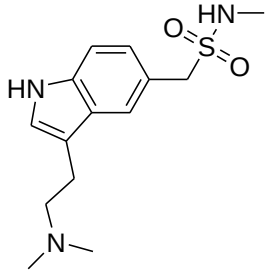
The Indole ring system represent plentiful and necessary hetero-cycle in surrounding. It is joined together in aromatic heterocyclic ring, consisting a ring of six-membered which is merged together with pyrrole ring having a bicyclic structure. The center of the atom of indole present in compounds are used to produce new products that possess interesting activities related to the body function of living things like antimicrobial, antioxidant, antidiabetic etc. Indole are used as starting material to create larger bioactive molecules.

Indole produced by a variety of bacteria because it is widely distributed in the natural environment. Indole is an intercellular signal molecule. It controls different parts of of bacterial physiology, including plasmid strength, spore construction etc. Serotonin, mitomycin C, vinblastine, reserpine are some natural occurring indoles.[1] Indole is generally found in body chemical that reduses stress and help with sleep, plant growth chemicals produced by the body (i.e. indole-3-acetic acid) brain chemical natural products and drugs.[2] Indole has little lower stabilization energy because indole undergo isoelectronic with naphthalene. Indole is very important in biological chemistry. Padalafil and fluvaspatin are the important drugs containing indole.

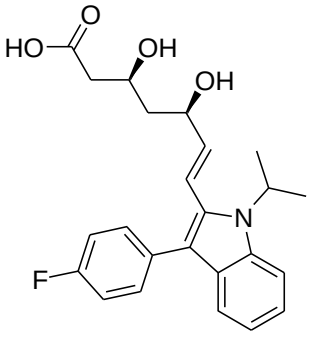
We have both kind of indole naturally occurring and produced by people. Indole can synthesised by many methods such as synthesis by fischer indole synthesis, vischler indole synthesis, hemetsberger, nenitzescuindole synthesis, Bartoli indole synthesis etc.[3]



Indole



Sumatriptan

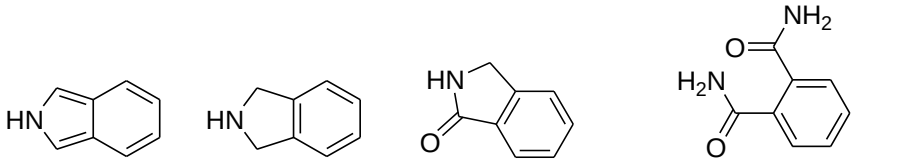


Fluvastatin

Isoindole is a compound which is an isomer of indole. Isoindole is also known as 2H-isoindole. It consists of six-membered benzene ring joined together with another ring which is five membered having nitrogen. Isoindole makes up similar structure of indole. The stable isoindole is formed by formal oxidation to the 10-system when the labile ortho-quinoid structure is deeply set within a π system.[4] The parent isoindole is rarely used but the substituted derivative of isoindole is important commercially and they are occurring naturally. The isoindole structure can be found in more than two, but not a lot of natural and drug-based compounds.[5-6] Some structures were explored from the isoindole such as isoindoline, isoindolinone, phethalimide, thalidomide, lenalidomide, pomalidomide, pigment yellow 139 etc. Diels-alder reactions are powerful method for synthesis of isoindole. It is also synthesised by flash vaccum pyrolysis of an N-substituted isoindoline and

dehydration of isoindoline-N-oxide. Isoindoles have many application such as they are used in material science, isoindole containing BODIPY dyes have been a lot used in different fields of science. These complexes are coloured and used as pigments. Isoindole was also showed a good example of medicinal chemist from astrazeneca in the synthetic pathway of mG1uR2 positive allosperic modulator.[7] 6-methoxy-2,5-dimethyl-2H-isoindole-4,7-dione was far apart from others and is known as the first naturally occurring isoindole. Isoindoline can also synthesized from isoindole which is fully reduced membered of isoindole family.[8]

By using isoindole we can synthesize isoindolinone (1,3-dihydro-2H-isoindole-1-one) by simply incorporation of added oxygen. Isoindolinones have a large scope in biological activities and present in natural product such as vitamin A, chilenine, linnoxamine, meagallanine.[9-12] Isoindolinones belong to the alkaloids family. Isoindolinone shows activities such as anxiolytic, antiangiogenic, anticlepresant, histone deacietylase inhibitory, TNFX α- inhibitory,[13-15] PARP-1-inhibitory[16] and cytotoxicity activity.[17]



isoindole isoindoline isoindolinone Phthalamide

AIM AND OBJECTIVE

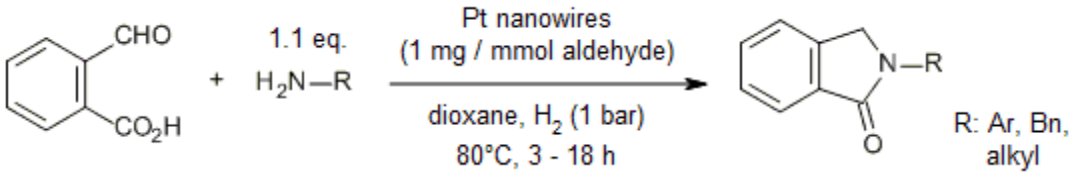
1. To synthesize Isoindolinone derivative with improved yield.
2. To study the mechanistic behaviour for the synthesis of isoindolinone.
3. To study the effect of various substituent on the chemical reactivity behaviour.
4. To develop the isoindolinone as a lead molecules for active study as CNS active agents.

REVIEW OF LITERATURE

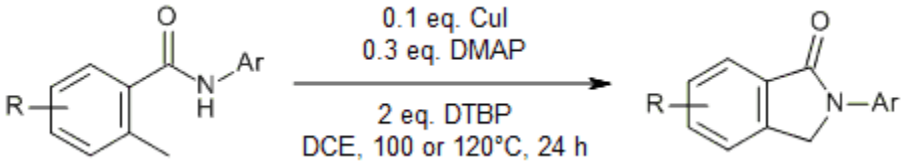
Isoindolinone is a heterocyclic compound which is formed from isoindole by simply incorporation of added oxygen. It contains both one or more hetero-ring having oxygen atoms as the only ring hetero atoms, and one or more ring having nitrogen as the only ring hetero atom containing two hetero rings linked by chain containing hetero atom as chain links. Isoindolinones belongs to the alkaloid family. It is found in natural products that has a wide range of biological activities such as antitumor, anticonvulsant[13-15]. Isoindolinone are interesting heterocyclic compounds due to their presence in many naturally occurring substances and because of their extensive use in medically helpful activities such as antihypertensive[18], antipsychotic[19], anaesthetic[20], and anti-leukemics properties[21].

Synthesis of Isoindolinone`s Derivatives

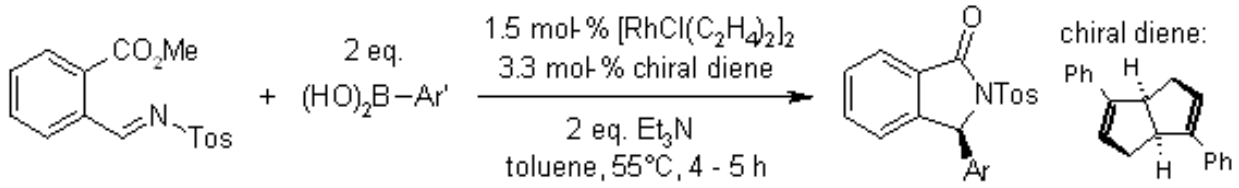
The reductive C-N coupling and intramolecular amidation of 2-carboxybenzaldehyde with amines in the presence of ultrathin Pt nanowires as catalysts under 1 bar of hydrogen is used to synthesise various N-substituted isoindolinones in excellent yields. Synthesis of phthalazinones can be done in high yield by these unsupported catalysts when hydrazine or phenyl hydrazine is used instead of amines.[22]



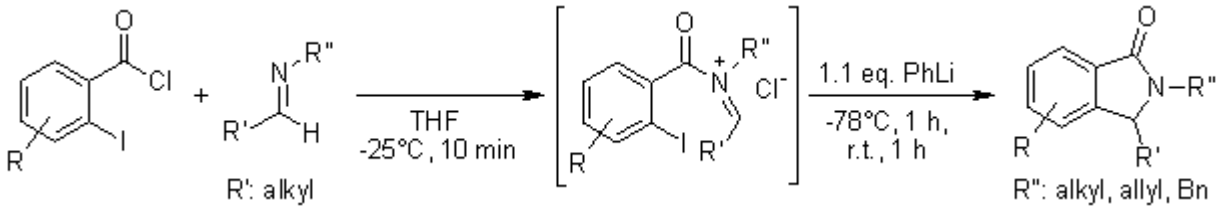
Various functionalized isoindolinones can be produced by using copper-catalyzed sp3 C-H functionalization of 2-alkyl-N-substituted benzamides.[23]



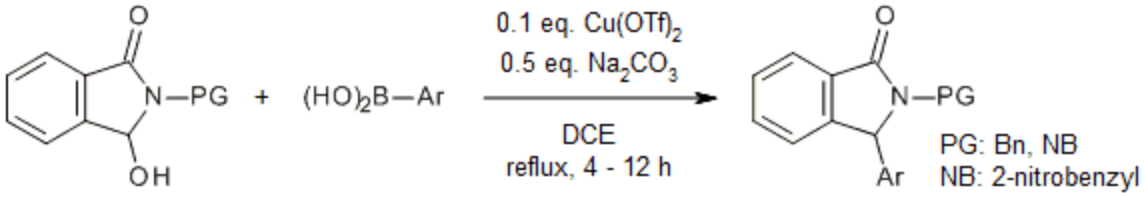
Rh-catalyzed asymmetric arylation of N-tosylarylimines with arylboronic acids gives a broad range of highly enantiomerically enriched diarylmethylamines as well as 3-aryl substituted phthalimidines and also a new type of C2-symmetric chiral diene ligand.[24]



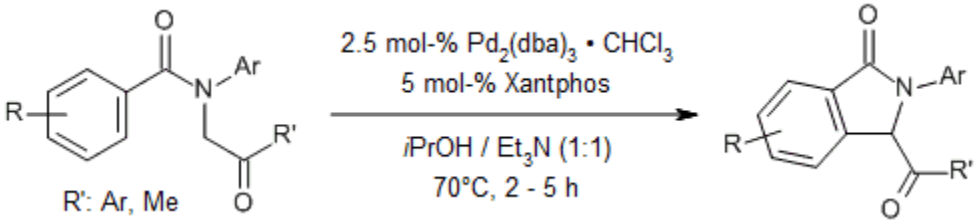
Addition of o-iodobenzoyl chlorides to imines affords N-acyliminium ions as adducts. Subsequent reaction of these adducts with phenyllithium at -78˚C followed by warming to ambient temperature induces an intramolecular Wurtz-Fittig coupling to afford 2,3-dihydroisoindolinones in excellent yields.[25]



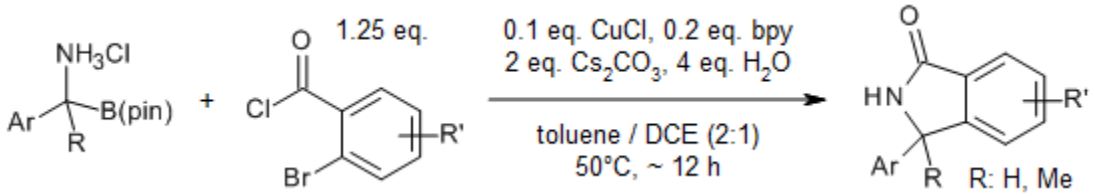
Copper(II) trifluoromethanesulfonate efficiently catalyzes the C-C coupling of 3-hydoxyisoindolinones with various aryl-, heteroaryl-, and alkenylboronic acids to furnish C(3)-substituted isoindolinones in 1,2-dicholoroethane (DCE) at reflux. The photolabile 2-nitrobenzyl protecting group is most appropriate for promotion of the coupling reaction and for deprotection.[26]



3-acyl isoindolin-1-ones and 3-hydroxy-3-acylisoindolin-1-ones can be produced with the help of an efficient palladium-catalyzed intramolecular cyclization of 2-iodobenzamides with a 2-oxoethyl function group on the nitrogen atom under mild conditions in good yield.[27]



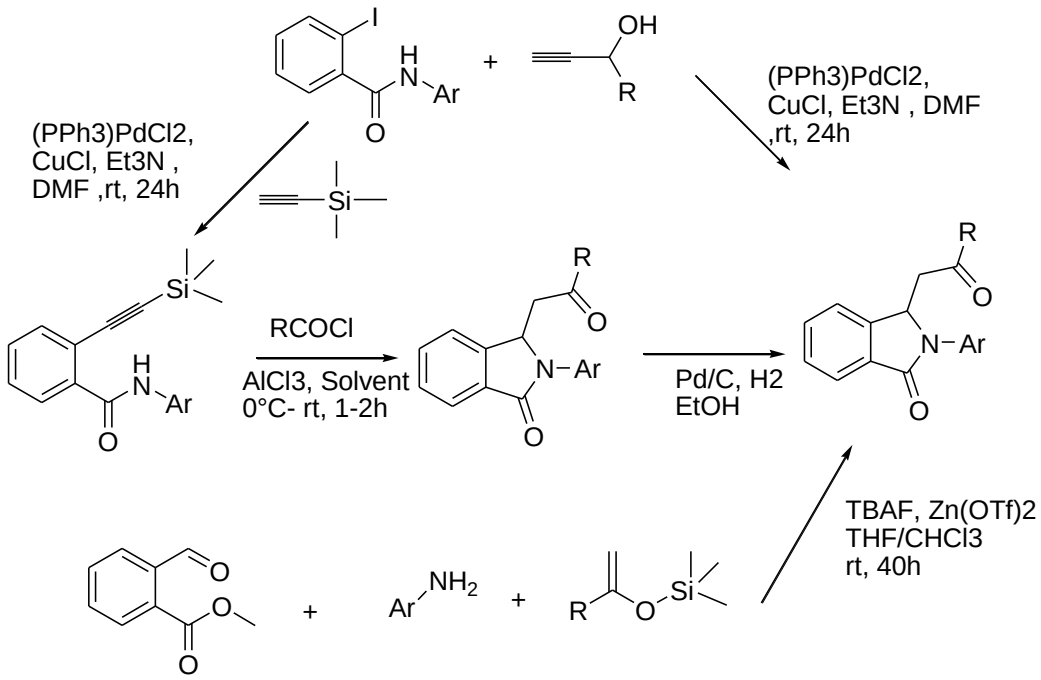
Acylation/Arylation reaction of α-aminoboronate salts with 2-bromobenzoyl chlorides under mild conditions via an intramolecular, Cu-catalyzed sp^3-sp^2coupling yields Isoindolinones.[28]



Substituted derivatives

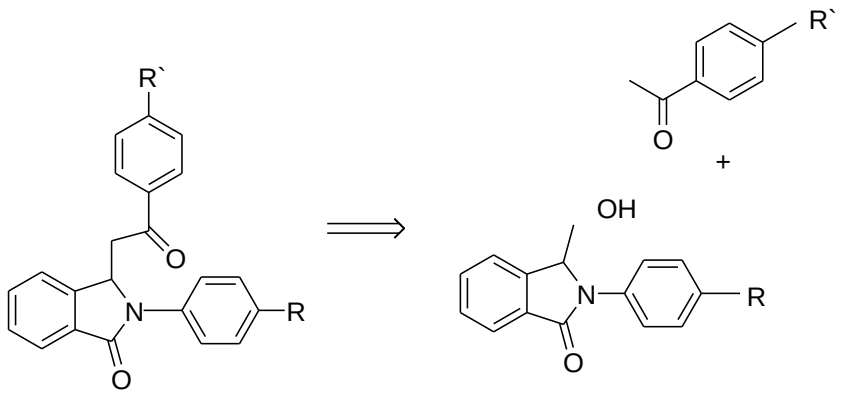
The reactions of 2-iodobenzamides with acetylenic carbinols using Pd as a catalyst having a acetylenic group which is present at terminal position attached with carbinol functionality next to the acetylenic gives the construction of 3-acylmethylisoindolin-1-one in one step.For getting product in single step the reaction involved sonogashira coupling which is followed by redox reaction and ring closure.[29]

Similarly from the same research group the reaction was done again between 2-iodobenzamides and trimethylsilylacetylene by using Pd as catalyst giving 2-(2-trimethylsilyl)ethynylbenzamides in excellent yield and after that by doing the Friedal-crafts reactions with acid chlorides or anhydrides under mild conditions smoothly giving the corresponding 3-alkylidene isoindolin-1-ones and then the double bond was removed by using Pd/C and H_2 to get the resulting isoindolinone[30].



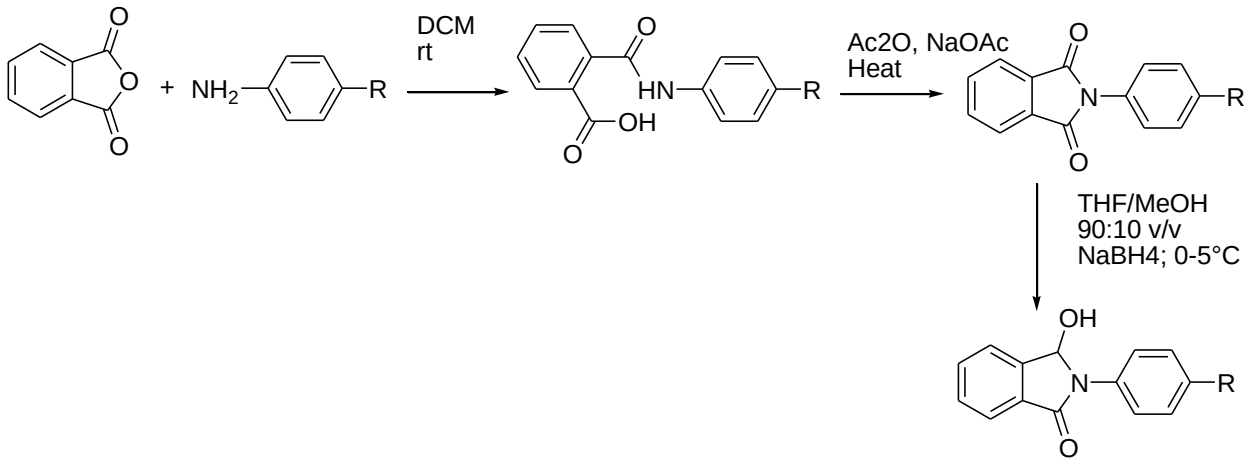
In the above methods for creation of isoindolinones there is a use of expensive catalysts and reagents, and multiple steps procedure are taken as a big disadvantages.[31-34]

For the development of cheap, less time consumer and green synthetic methodologies the another method was reported in which the starting metrial was 3-hydroxy-2-arylisoindol-1-ones and low cost alkyl aryl ketones are used.[35]



Retrosynthesis analysis

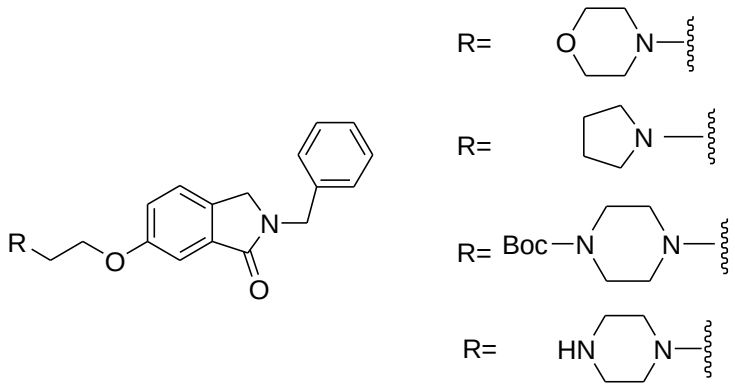
The reactions of phathalic anhydride with anilines give the similar 2 (arylcarbanoyl) benzoic acid in good yield. In 2nd step the N-aryl-1H-pyrole-2,5-diones is formed as a product by acylation with acetic anhydride and sodium acetate. And by doing reduction of above compound with $NaBH_4$ we can obtained the desired 3-hydroxy-2-arylisoindol-1-ones in very good yield.



The mechanism for this reaction appears to be straight forward almost the same as mannich reaction n-acyliminium ions are formed by the treatment of N-acyl-3-hydroxyisoindolinones with $Cu(OTF)_2$. The attack of nuecleophile is on position where enol is attached in N-acyliminium ion.[36]

Novel Anticancer isoindolinone derivatives

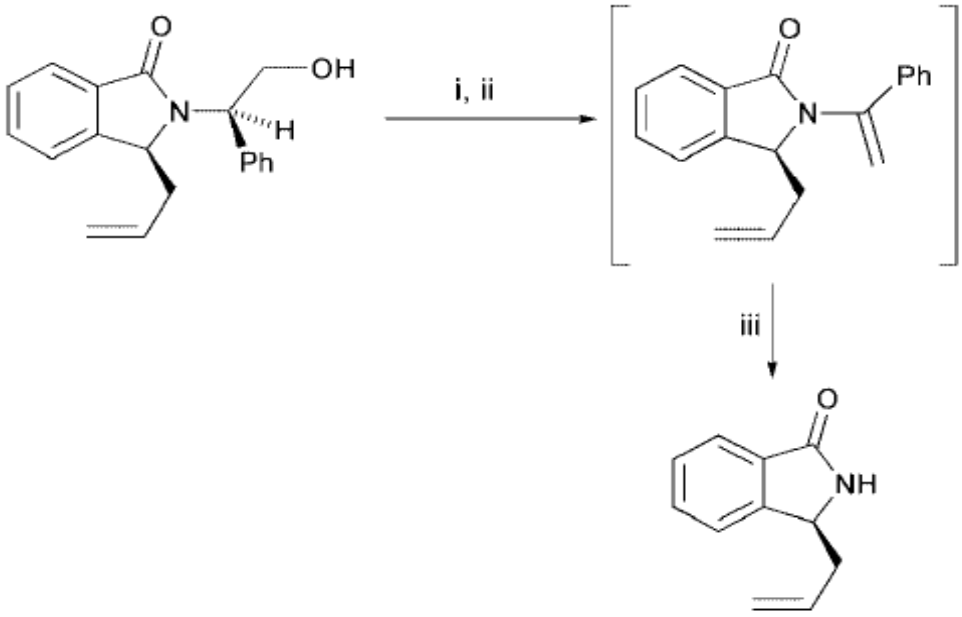
Cancer is a worldwide public health problem. The World Health Organization guesses of a number that there are about 10 million new cancer patients each year. Now, cancer rate at which people die is still on the rise. The existing chemotherapy drugs in clinical with the using of anti-cancer drugs, the resistance of existing chemotherapy drugs have slowly came out in clinic, this way there is an extremely importent need for new effective anti-cancer drugs.There are some isoindolinones derivatives which is used as novel anticancer target molecules.The synthesis of these derivatives are given in 8 steps with nucleophile substitution reaction and cyclization.[37]



Synthesis of 3-substituted 2H-isoindolin-1-one

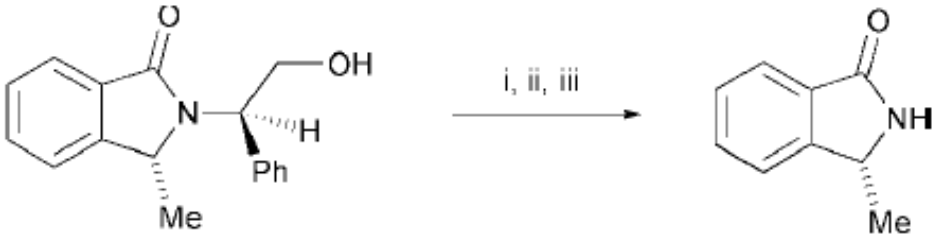
The synthesis of non-racemic 3-substituted 2H-isoindolin-1-one molecule can be done by different routes. Here we will demonstrate novel routes for prepration by removing the chiral of auxiliary.

The reaction was started by using 2:1 mixture of diastereoisoers and to obtain final product some reagnets were added at different steps. The reaction is completed in two steps and carried out at 80°C. At the end of reaction we get the final product 3-substitutedisoindolinone in good yield.



Reagents and conditions: i, $MeSO_2Cl$, Et_3N; ii, NaOEt, EtOH; iii, 3 M HCl, EtOH–H_2O, 80 °C.

The above procedure are worked well and gives good yield and therefore second method was also done by same procedure but by taking different substrates as a starting material.



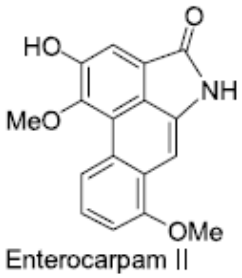
Reagents and conditions: i, $MeSO_2Cl$, Et_3N; ii, NaOEt, EtOH; iii, 3 M HCl, EtOH–H_2O, 80 °C.

In this method the reaction is done by treating starting compounds with conc. H_2SO_4 and this mixture was heated in boiling water bath to get the desired target molecule.[38-39]

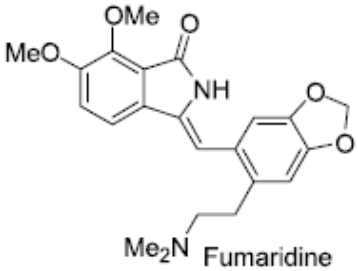
Reagents and conditions: i, conc. H_2SO_4; ii, H_2O.

Naturally occurring and biologically active substituted 3-methyleneisoindolin-1-ones

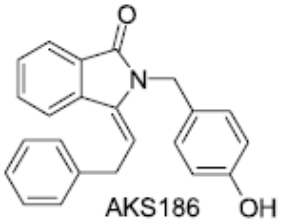
3-methyleneisoindolin-1-ones is a substituted derivative of isoindolinone which are very important for their biological use and natural occurance. It is found in many naturally products such as Enterocarpam, which is the member of aristolactam alkaloids family. It is also seen in the Fumaridine. This type of derivative of isoindolinone are also found in biological active compounds such as AKS186 which is helpful to display vasorelaxant.[40]



Enterocarpam II

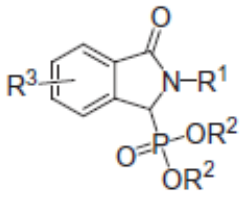


Fumaridine

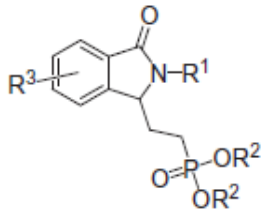


Phosphorylated Isoindolinone Derivatives

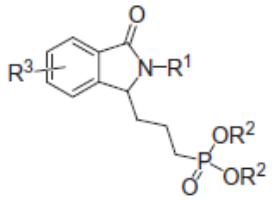
Phosphorylated Isoindolinone Derivatives compounds have attracted attention due to their potential biologic activity or as structural blocks for designing bioactive compounds.[41-42]
Some examples are 3-oxoisoindolin-1-yl-phosphonates-1-yl-phosphonates, Diethyl [2-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)ethyl]phosphonates, diethyl [3-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)propyl]phosphonates.



3-oxoisoindolin-1-yl-phosphonates-1-yl-phosphonates

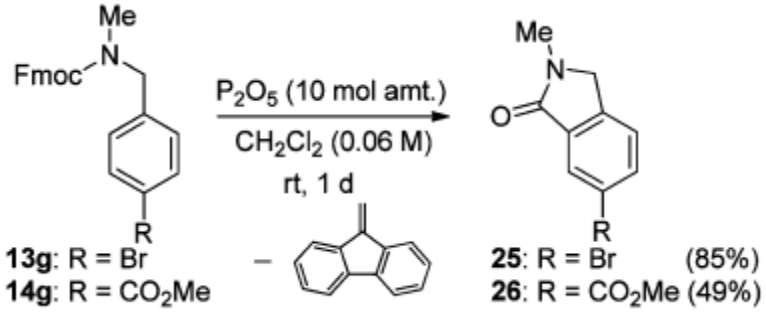


diethyl [2-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)ethyl]phosphonates

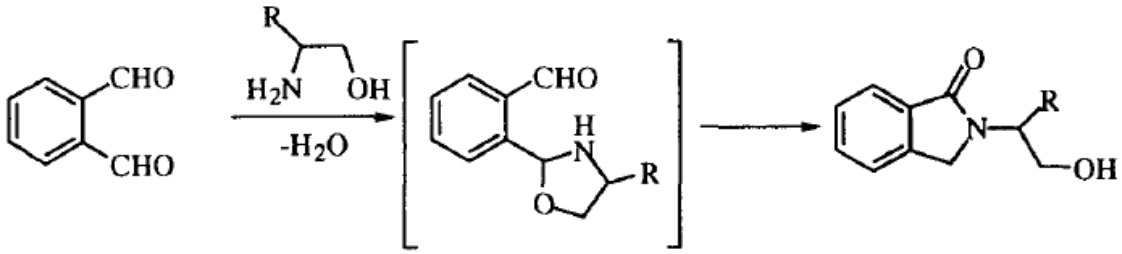


diethyl [3-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)propyl]phosphonates

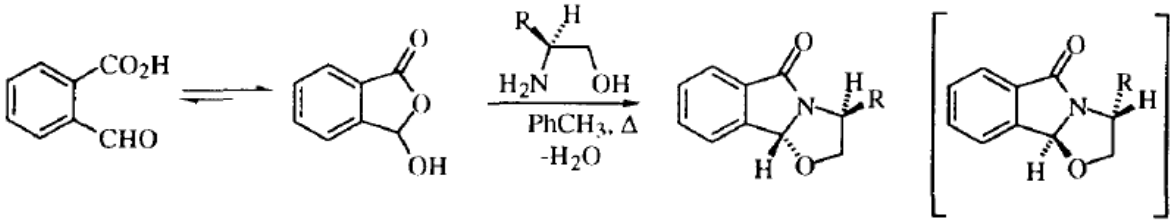
Isoindolinone can be obtained by using the method that lead to the use of Fmoc-benzylamines as a compliment to the construction of isoindolinone with electron deficient aryl groups. This is the simple and versatile method which is related to divergent synthesis demanded by drug-based pharmaceutical developments and natural product synthesis.



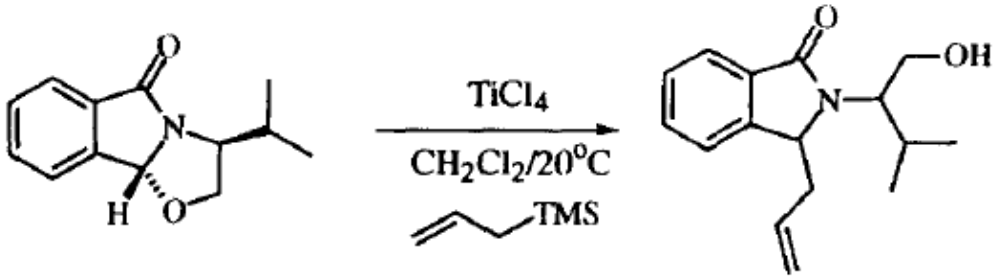
Isoindolinone derivatives are also obtained by direct condensation of ortho-phthaladehyde with amino alcohol in the presence of external synthetic auxiliary we have proposed method involving neighboring group assistance by the alcohol functional group.



The reaction was done between alpha- amino alcohols and 2-formylbenzoic acid. To proceeds the reaction equimolar amounts of the mixture of two components were heated at reflux in toluene solvent to obtained desired product.



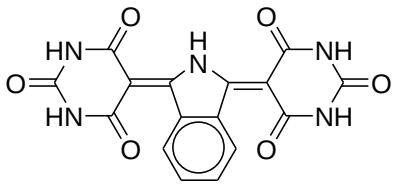
The (+/-)-valinol derived tricyclic lactum was treated with titanium tetrachloride at room temperature in dichloromethane prior to addition of allyl trimethylsilane to yield the desired substituted isoindolinone in 96% isolated yield.[43]



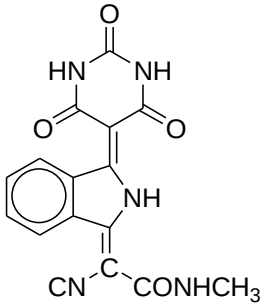
Commercially available isoindolinone and isoindolinone pigments and their applications

Commercially available pigments of isoindolinone are yellow representatives such as pigment yellow 109, pigment yellow 110, pigment yellow 139, pigment yellow 173 and pigment yellow 185, pigment orange 61, pigment orange 66, pigment orange 69, pigment red 260, and pigment brown 38.Pigments providing other shades have failed to gain much commercial impact.

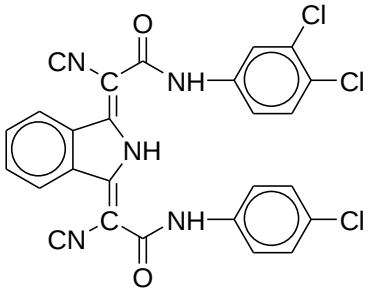
Examples of pigments:



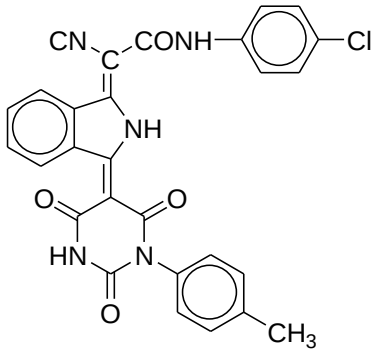
Shade - reddish yellow
Pigment yellow 139



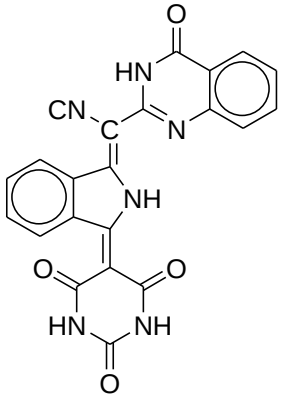
Shade - greenish yellow
Pigment yellow 185



Shade - yellowish orange
Pigment orange 66



Shade - yellowish orange
Pigment orange 69



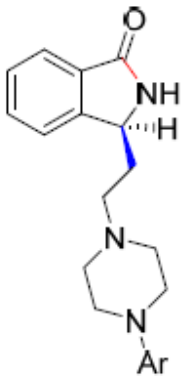
Shade - yellowish red
Pigment red 260

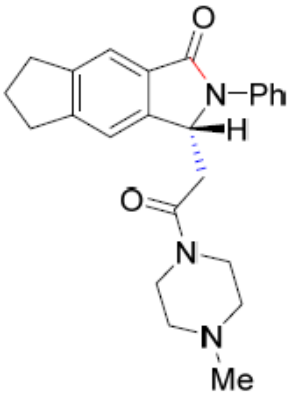
Pigment Yellow 109 is used in plastics, paints, and printing inks. Combination of inorganic pigments with pigment yellow 109 deeply imparts colors on automobile finishes. P.Y. 109 is fast to over-coating, its heat stability satisfies almost all requirements. Weather-fast and lightfast property of Pigment Yellow 110 is preferable for automotive finishes. Due to its high transparency, it is used in metallic shades. It has use in emulsion paints and in architectural paints. It fulfills the need for longterm exposure. Pigment Yellow 139 has average tinctorial strength in plastics. Inflexible needs are not satisfied as it is not so durable. Higher temperature makes its color duller that results in pigment decomposition. Pigment Yellow 185 has application in packaging printing inks. It has perfect quality of fastness to over-coating. Due to poor weather-fastness of these coatings, it is mainly used for indoor applications, especially in good value powder coatings, if weather-fastness and high light-fastness are not required. Pigment Orange 61 is preferred as a colorant for polystyrene, unsaturated polyesters, polyurethane, and elastomers. Good lightfastness and high heat stability make it suitable for spin dyeing polyacrylonitile and polypropylene.Pigment Orange 66 has high tinctorial strength. Excellent weather-fastness and light-fastness makes it applicable to use in high grade industrial especially in original automatives. [44-47]

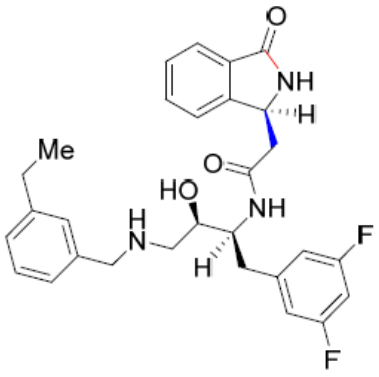
Biological activities of Isoindolinones

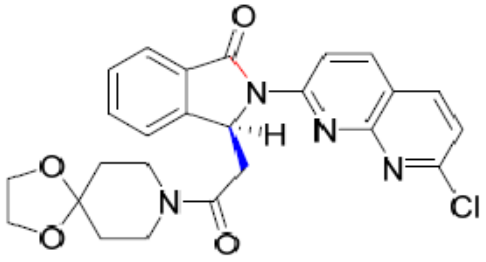
There are many uses of isoindolinones in medicinal chemistry. Isoindolinones are used as medicines and also for manufacturing different medicines.

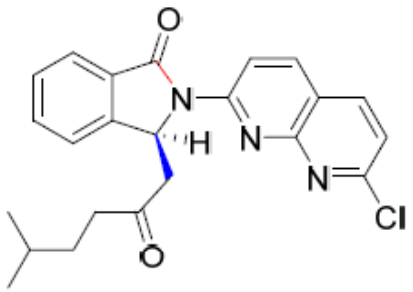
Isoindolinones are heterocyclic compounds having potential biological activities, such as anti-hypertensive (high blood pressure), anti-psychotic, anti-inflammatory, and pain killer. Some members of this class of heterocyclic support also display anti-ulcer, vasodilatory, anti-viral, anti-leukemic properties, and platelet aggregation inhibitory activities.
These are also found to cause dose-dependent p53-dependent tiny chemical assembly transcription in MDM2-amplified SJSA human sarcoma cell lines.
Also, isoindolinones are useful in the production of different drugs and complex natural products. Since enantiomers interact differently with the biological system, therefore, intense research is going on to create these biologically active isoindolinones in enantioenriched form.
In fact, (*S*)-PD 172938 is reported as a strong (brain chemical) D4 ligand, and (*R*)-JM 1232 is a benzodiazepine receptor agonists for the treatment of anxiety, whereas is an inhibitor of the β-secretase enzyme for the treatment of Alzheimer's disease.





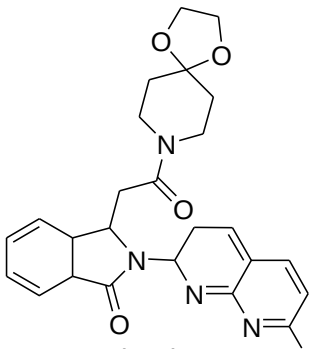




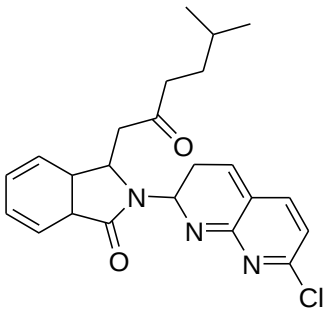


Isoindolinones goes through some process to give these medicinal compounds, those processes are given as Heck cyclization, Diels-Alder approach, domino three-component coupling lactamization, ring closure of chiral hydrazones, reactions of chiral acyliminium ion, allylation to chiral imines, azaconjugate addition, and chiral appendage mediated carbanion method. Transition-metal catalyzed processes include, Rh(I)-catalyzed arylation,21a Cu(I)-catalyzed tandem Michael-Mannich reaction,21b Pd(II)-catalyzed aza-Wacker type cyclization21c and organocatalytic syntheses include thio-urea catalyzed malonate addition,22 our direct organocatalytic Mannich-lactamization,23 and phase transfer catalyzed aza-Michael reactions.[48]

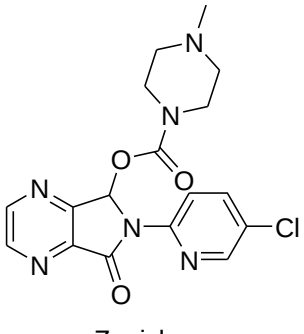
Some substituted isoindolinones possess anxiolytic hyprotics, antihypertensive, antipsychotic, antiflammatory, anaesthetic, antiulcer, vasodilatory, antiviral, antileulcemic and muscle relaxants. Typical examlpes are pazinaclone, pagoclone and zapiclone. We can synthesise these types of substituted isoindolinones by several procedures.



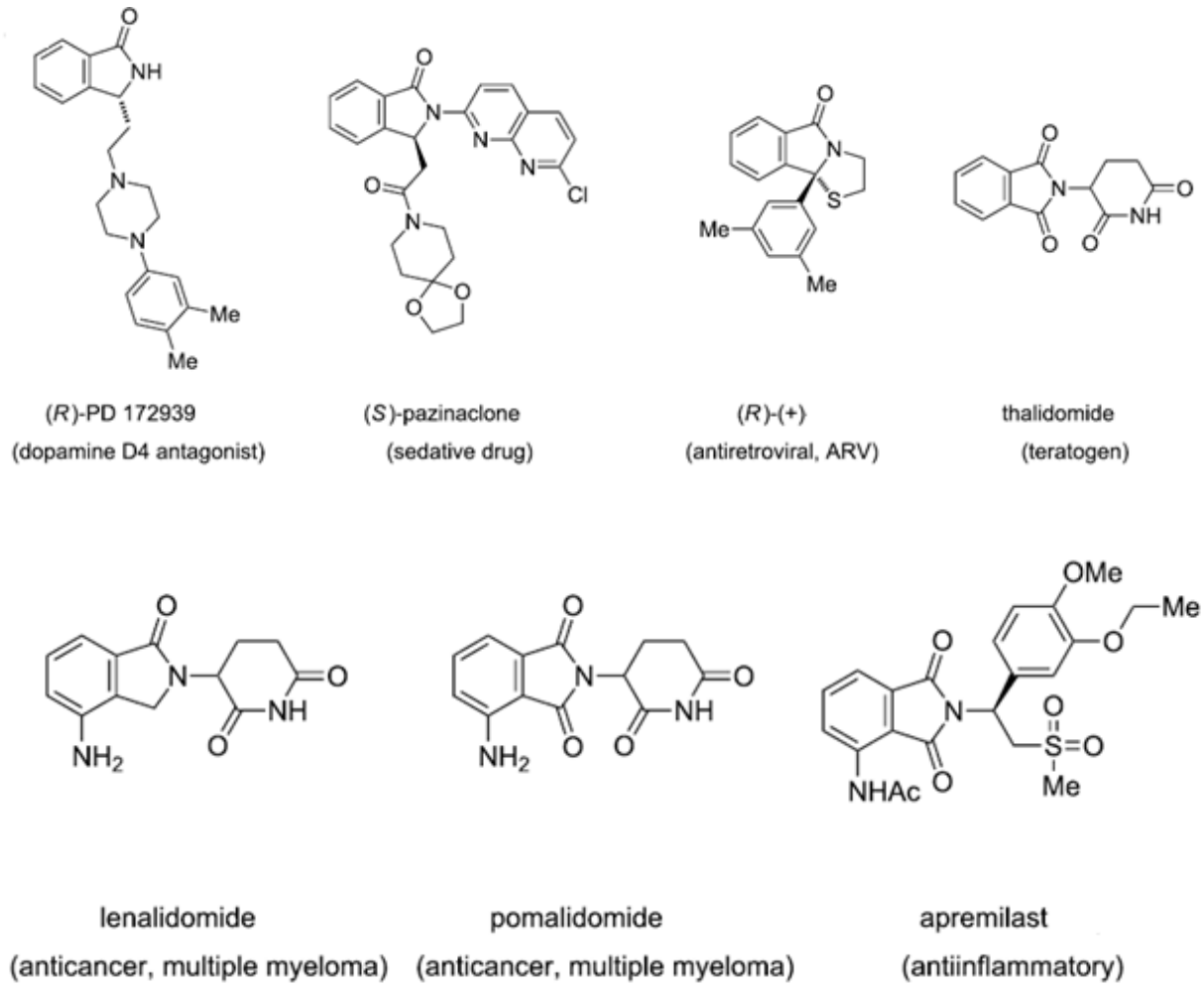
Pazinaclone



Pagoclone

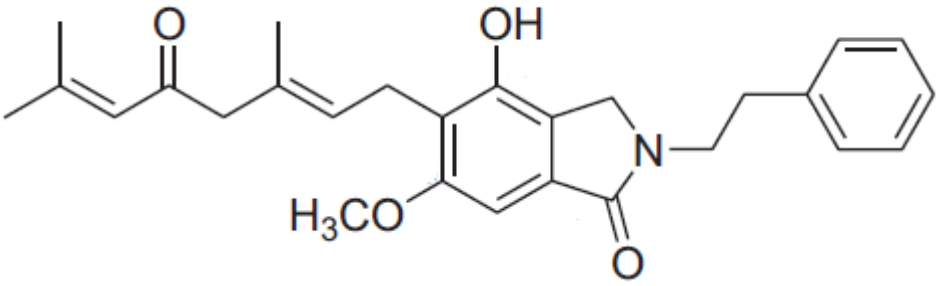


Zopiclone



Structures of bioactive substituted isoindolinone

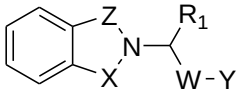
Isohericenone is also very useful for its activity related to the body function of living things. It is a new cytotoxic isoindolione alkaloid from Hericium erinaceum. These Korean wild mushrooms are collected and figured out the quality of their MeOH extract for their antitumor activity. Among the all collected wild mushrooms, the extract of Hericium erinaceum showed significant cytotoxicity against A549,SK-MEI-2 and HCT-15. This mushroom has been used as a medicine or the treatment of dyspepsia (heartburn), gastic ulcer and enervation in traditional Chinese medicine for a long time.[49]



Isohericenone

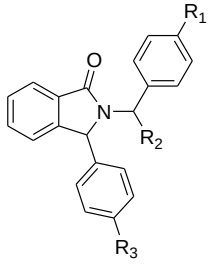
Novel 1,2-benzisothiazolinone are also very important compound which is useful due to medicinal properties. The composition of 1,2-benzisothiazolinone and isoindolinone compounds are very useful in treating, and preventing from viral infections such as Hepatitis C virus and flavivirus infections , and yeast infection or fungal problem such as asperillosis and candidiasis.

A first class of compound includes these type of composition is given as



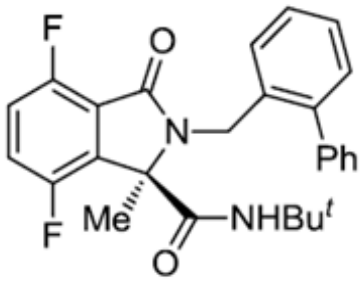
Where R_1= hydrogen or methyl; W = -C(O)NR2-, -C(O)NR3-NR4C(O)- ; X = CH2 or S; Y is hydrogen , hydroxyl , alkoxy and Z is C=O or SO_2

3-aryl isoindolinone is also related to the body function of living things and this compound is also used for the treatment of many sciknesses and medical problems.[50]

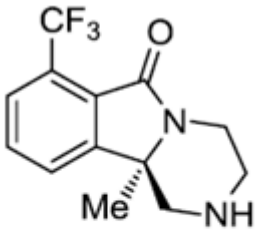


R_1= -OMe, -NO_2, -NHAc;
R_2= -$(CH_2)_n$OH, -$(CH_2)_n$COOMe, -CH_2NH_2, -CH_2COOH, -CH_2CONH_2;
R_3= -Me, -OBn, -OH, -OPh, isobutoxy

Isoindolinone bearing amine functionality are an important skeleton. These are used in biological active natural products and drugs such as drug for the treatment of cardiac arrhythmias (unsteady heartbeats) and a modulator of serotonin receptors.[51]



treatment of
cardiac arrhythmias

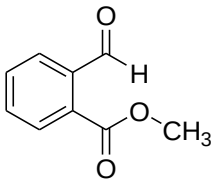


modulator of
serotonin receptors

Isoindolinone is also act as novel metabotropic glutamate receptor 1 antagonists which is very helpful in possible treatment for seriously mentally ill problems. Glutamate is acompound which is present in the central nervous system (CNS) as one of the major excitatory neurotransmitter. The ionotropic glutamate receptors such as NMDA and non-NMDA receptors and the G-protein coupled metabotropic glutamate receptors is influenced by glutamate. These all have very important in pharmacologicl properties. mGluR5 are used as drug targets or controling glutamate transmission in the treatment of different nerve-based and psychiatric sciknesses such as dangerous overuse of drugs, schizophreniar (very serious mentl disorder), pain, fear and stress and epilepsy. As a result , many isoindolinone derivatives can showed single digit mGluR1 antagonistic activity, sufficient selectivity for mGluR5 and also preferable for oral CNS drugs, and also good metabolic stability.

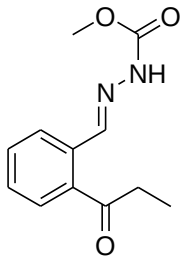
EXPERIMENTAL

Prepration of methyl 2-formylbenzoate



To the clear solution of Carboxylbenzaldehyde (2g, 0.0133 mol) and methyl iodide (2.39g, 0.016 mol) in dry acetone (60ml) in RBF was added potassium carbonate (1g) . The contents were heated and stirred on magnetic stirrer for 3-4 hours under anhydrous condition . Progress of the reaction was monitored using TLC (chloroform: ethylacetate). After the completion of reaction TLC, solvent was evaporated under reduced pressure to obtain solid mass which was tinctured with diethyl ether (5×2 ml) and product was dried to obtain pale yellow solid(1.6 g).

Prepration of (E)-mehyl 2-(2-(methoxy carbonyl) benzyene) hydrazine carboxylate



To the clear solution of methyl 2-formylbenzoate (0.5g, 0.003 mol) and methyl hydrazinocarboxylate (0.032g) in dry methanol (10ml) in RBF was added zincperchlorate (1g). The solution was stirred on magnetic stirrer for 2 hours at room temperature. Progress of the reaction was monitored using TLC (chloroform: ethylacetate). After the completion of reaction TLC, solvent was evaporated under reduced pressure to obtain solid mass which was tinctured with diethylether (5×2 ml) and the product was dried to obtain white solid(0.3g).

IR Data :

1715 C=O

3037 C-H

3161 N-H

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