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A Comprehensive Review On SAR And Activities Of Isoindolinone

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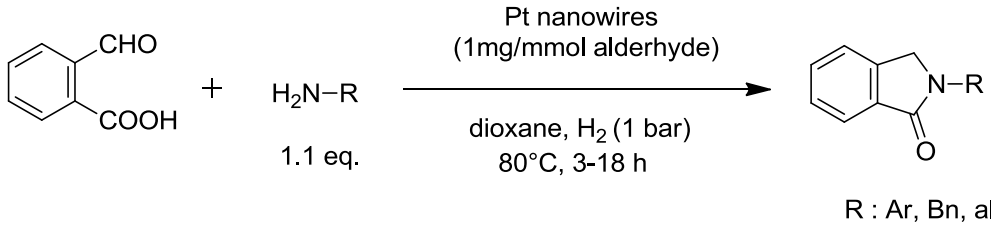
Abstract: For the various biological activities a lot of compounds of natural and synthetic origin have been used to treat upon various ailments, these compound have been either isolated from natural sources, synthesized chemically or are modified using different precursors, the present report provides a report on the synthesis and activities of compounds which have synthesized chemically to get variety of biological functions. Major emphasis in this report lies around the identification of synthetic methodologies adopted for the synthesis of these compounds.

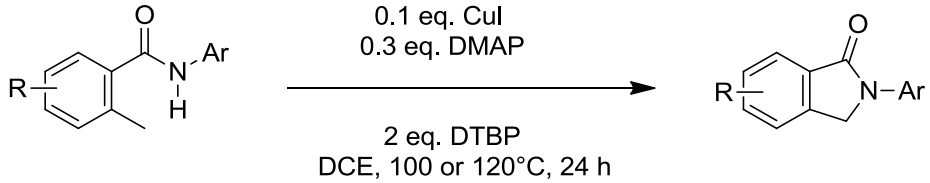
Introduction:

Isoindolinone is an alkaloid based heterocyclic compound which is of interest due to its structural and biological functions which carries hetero-ring that contains oxygen and nitrogen which are joined together in the form of chain links. It play an important role in many biological activities such as anticarcinogenic, anticonvulsant and many others[1-3]. Isoindolinone are fascinating used extensively in pharmacological activities such as antihypertensive[4], antipsychotic[5], anaesthetic[6], and anti-leukemic properties.[7-10] In order to synthesize these compound a variety of synthetic methodologies have been adopted, present report will deal with compilation of these methodologies for the synthesis of these compounds.

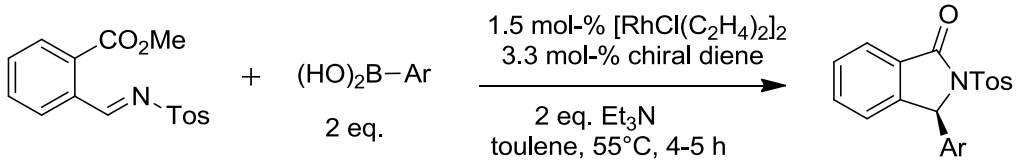
Synthesis of Isoindolinone Derivatives



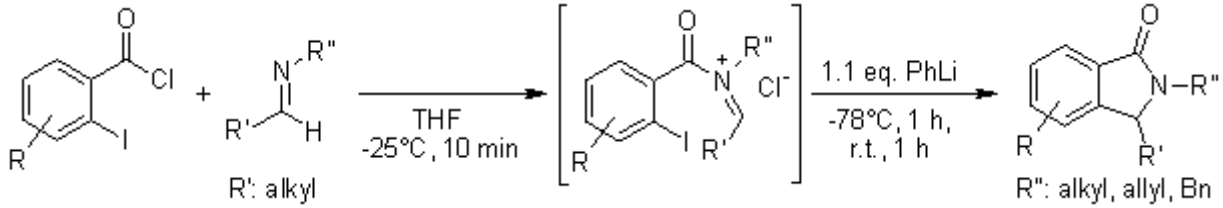
The C-N coupling which is of reductive nature and the amidation that occurs inside the molecules of 2-carboxybenzaldehyde with amines, Pt-nanowires in the form of catalysts is used under the pressure of 1 bar of hydrogen is used to synthesise various N-substituted isoindolinones in plentiful amount of yield. Synthesis of phthalazinones can be done in high yield by these unsupported catalysts when phenyl hydrazine or hydrazine is used in place of amines.[11]



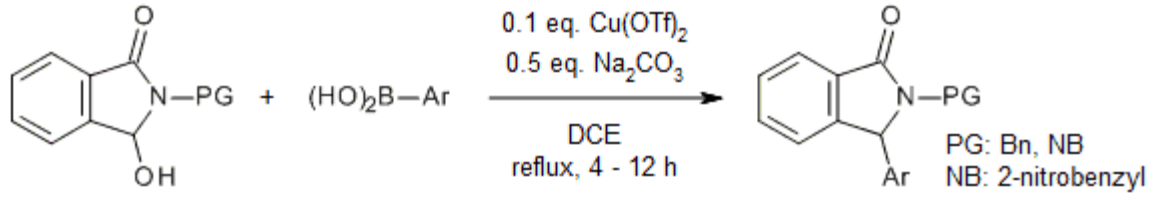
Various functionalized isoindolinone can be produced by using copper-catalysed sp3 C-H fictionalizations of 2-alkyl-N-substituted benzamides.[12]



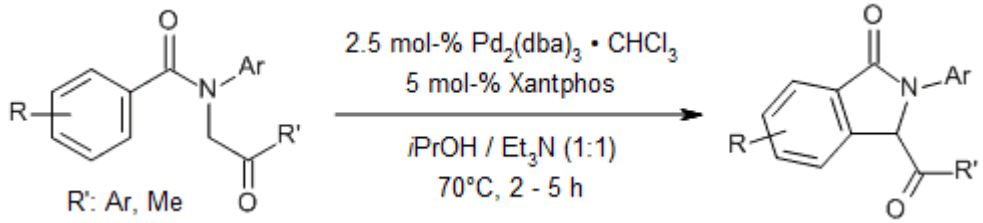
Asymmetric arylation of N-tosylarylimines which is Rh-catalysed, with arylboronic acids furnishes a range of highly enantiomerically enriched diarylmethylamines along with 3-aryl substituted phthalimidines and also a novel version of C2-symmetric chiral diene ligand.[13]



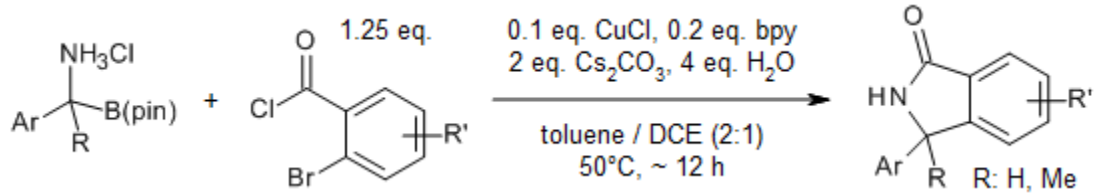
Upon the reaction of o-iodobenzoyl chlorides with imines affords N-acyliminium ions as adducts. Which upon reaction with phenyl lithium at -78˚C accompanied by maintaing ambient temperature induces an intermolecular Wurtz-Fittig coupling to produce 2,3-dihydroisoindolinones in plentiful and copious yields.[14]



Copper (II) trifluoromethanesulfonate efficiently carries out the catalytic reaction of C-C joining of 3-hydoxyisoindolinones with various aryl-, heteroaryl-, and alkenylboronic acids to yield isoindolinones in 1,2-dicholoroethane (DCE) at reflux. The light unstable 2-nitrobenzyl protecting group is most suitable for coupling reaction and for deprotection.[15]



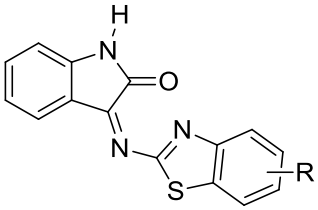
3-acyl isoindolin-1-ones and 3-hydroxy-3-acylisoindolin-1-ones can be produced with the help of an efficient reaction that is catalysed by palladium and there is cyclization within the molecules of 2-iodobenzamides with an addition of 2-oxoethyl function group on the atom of nitrogen under mild conditions in good yield.[16]



Acylation/Arylation reaction of α-aminoboronate salts with 2-bromobenzoyl chlorides under mild conditions via an intermolecular, Cu-catalyzed sp^3-sp^2coupling yields Isoindolinones.[17]

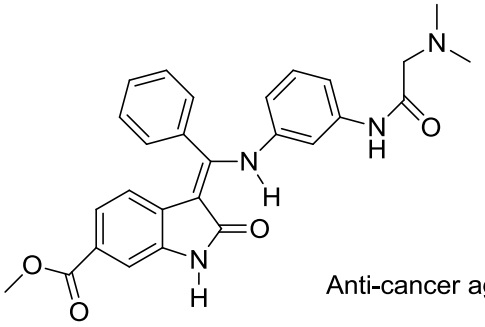
Synthesis of substituted indolinone derivatives

Dissolution of 6-substituted 1,3 benzothiazol-2-amine and indole 2,3-dione in absolute methanol gives Schiff base as the final product. Schiff base is used as anti- tumour agent.



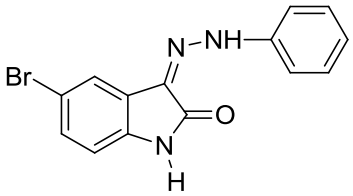
R = Me, i-pr

For apoptosis of acute myeloid leukaemia cell and growth inhibition, a large number of new indolinone derivative are synthesized. For targeting vascular endothelial growth factor, platelet derived growth factor and fibroblast growth factor, these derivatives are used.[18]

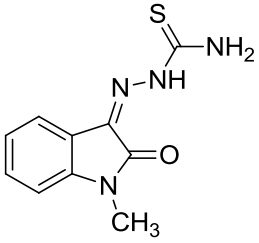


Anti-cancer agent

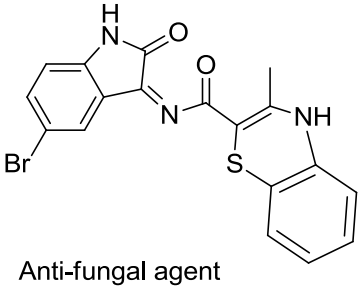
Various significant pharmacological activities such as, anti-fungal agent, anti-cancer drug, tuberculostatic agent, active agents of AIDS and anti-viral methisazone are shown by some isoindolinone compounds.



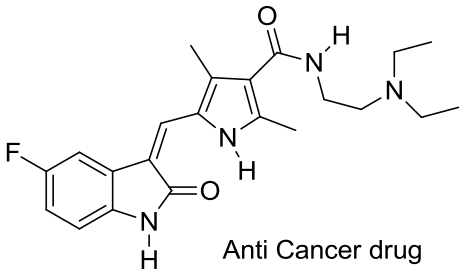
Tuberculostatic agent



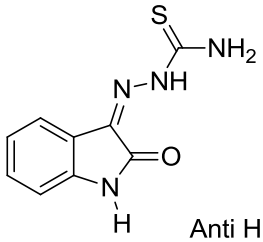
Anti-viral Methisazone



Anti-fungal agent

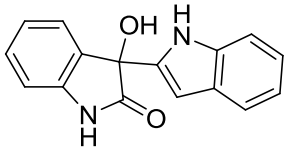


Anti Cancer drug



Anti HIV

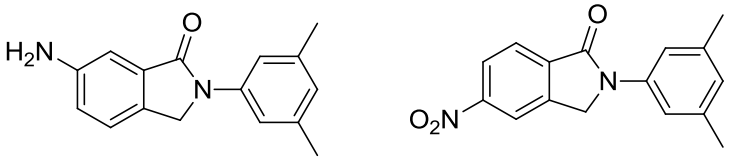
For the treatment of cancer, N-substituted isatin have been used as intermediate for different heterocyclic compounds. At selective conditions only, some of the isatin derivatives are synthesized.[19]



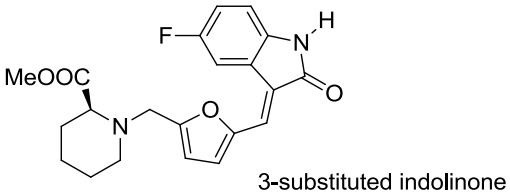
substitute derivative.
act as anticancer drug

The enzyme through its active sites gets easily bounded with the substrate is known as cyclooxygenase. There are two isoforms of COX i.e. COX-1 and COX-2. The given two

compounds out of several isoindolinone compounds show maximum effective inhibition activity on COX-1 and COX-2.[20]

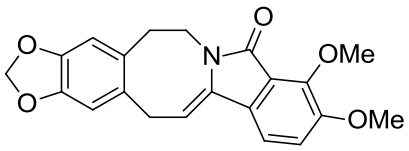


On the basis of molecular docking phenomenon, PTP 1B inhibitors is a noble series of heterocyclic derivative which is known as protein tyrosine phosphate 1B inhibitor.

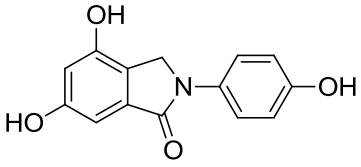


3-substituted indolinone

Isoindolinone derivatives as CNS active agents



Anti-inflammatory

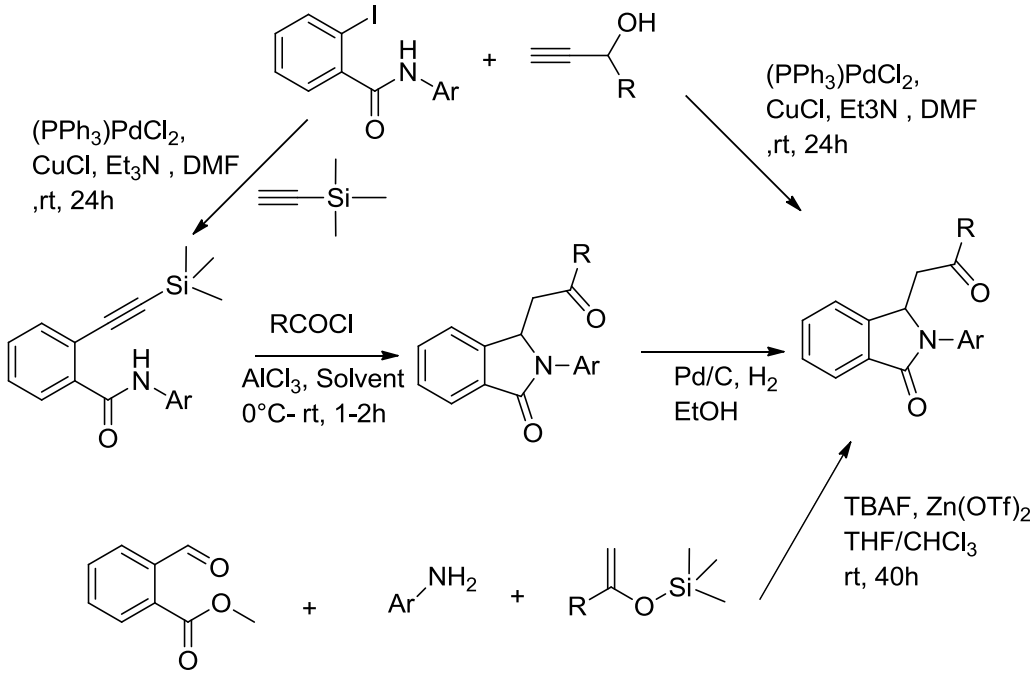


Anti-hypertensive agent

Synthesis of isoindolinone derivatives

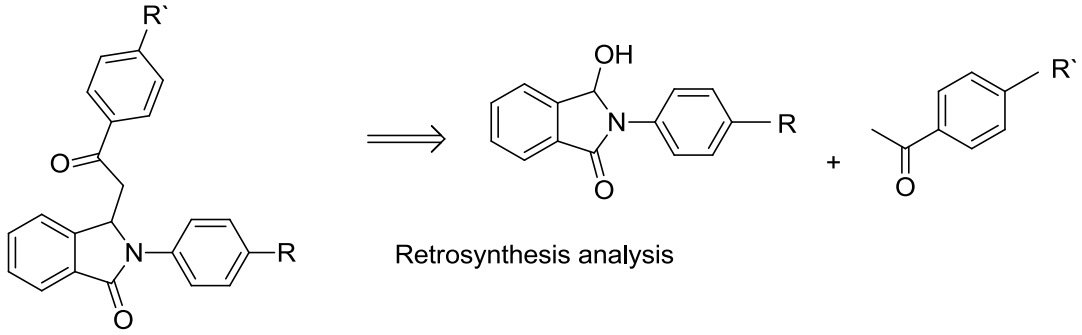
2-iodobenzamides is made to react with the acetylenic carbinols using Pd as a catalyst having a acetylenic group which is present at terminal position attached with functionality of carbinol alongside the acetylenic gives the construction of 3-acylmethylisoindolin-1-one in one step.[19] The product formation involves sonogashira coupling which is followed by redox reaction and ring closure through a single step.[21]

Similarly, the reaction has been carried between 2-iodobenzamides and trimethylsilylacetylene by using Pd as catalyst giving 2-(2-trimethylsilyl) ethynylbenzamides in excellent yield. Involving Friedel-crafts reaction with acid chlorides or anhydrides easily giving the equivalent 3-alkylidene isoindolin-1-ones and then the covalent bond was removed by using H_2 and Pd/C to get the resulting isoindolinone.[22]



The reaction is carried over involving a multiple synthetic techniques and involvement of catalyst so as to afford the desired products in quantitative yields.

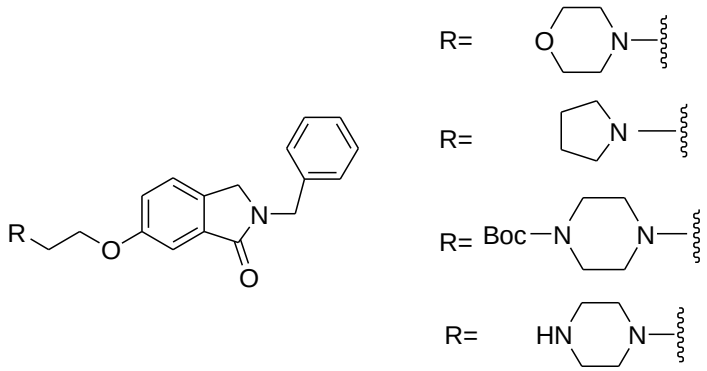
For the development of cheap, less time consumer and green synthetic methodologies, another method was reported in which the starting material was alkyl-aryl-ketones which has low cost and 3-hydroxy-2-arylisoindol-1-ones are used.[23]



The reactions of phthalic anhydride with different anilines give the corresponding 2 (arylcarbanoyl) benzoic acid in quantitative yield. N-aryl-1H-pyrole-2,5-diones is formed by acylation with sodium acetate and acetic anhydride and by reduction of above compound using $NaBH_4$.[21]

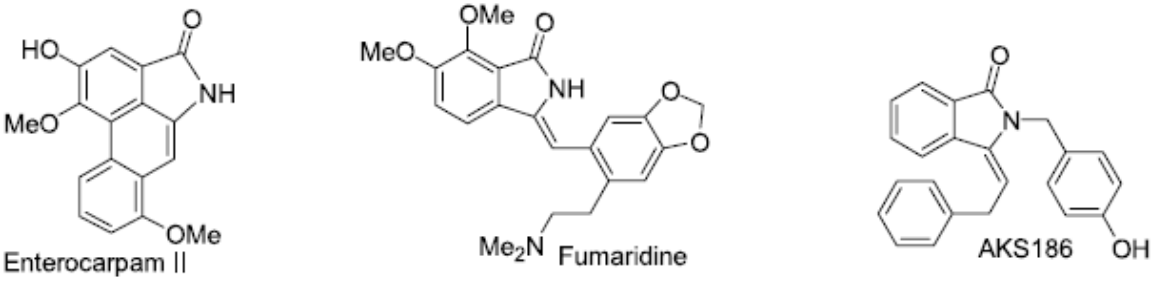
Anticancer isoindolinone derivatives

Cancer is a serious health problem which has its root in the whole world. Every year around 10 million new cancer patients are identified as per the reports of the World Health Organization. Now rate at which people die because of cancer is rising every year. There are some isoindolinones derivatives which is used as novel anticancer target molecules. The synthesis of these derivatives are given with nucleophile substitution reaction and cyclization.[25]



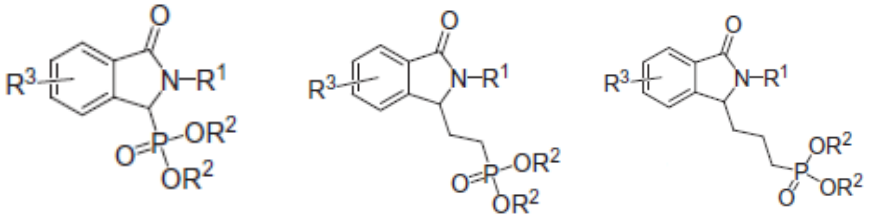
Naturally occurring and biologically active substituted 3-methyleneisoindolin-1-ones

3-methyleneisoindolin-1-ones is a substituted derivative of isoindolinone which are very important for their biological use and natural occurrence. It is found in many naturally products for example Enterocarpam, which is the part of aristo lactam 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.[26]

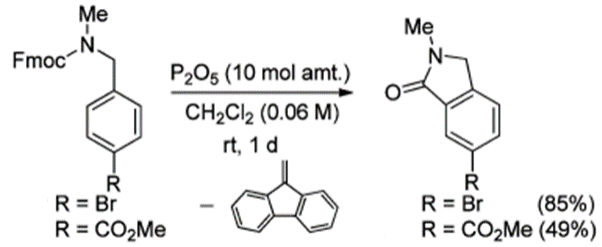


Phosphorylated Isoindolinone Derivatives

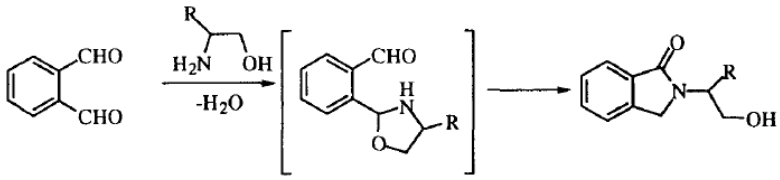
Phosphorylated Isoindolinone derivatives identified due to their potential biological activity or as building blocks for synthesis of bioactive compounds.[27] Some examples are 3-oxoisoindolin-1-yl-phosphonates-1-yl-phosphonates, Diethyl [2-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)ethyl]phosphonates, diethyl [3-(2-alkyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)propyl]phosphonates.[28]



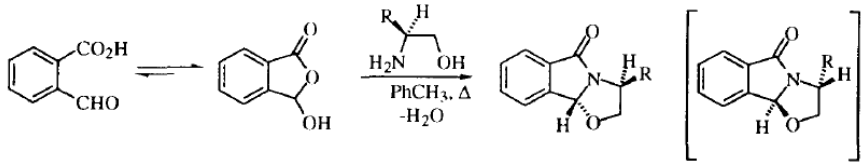
Isoindolinone can be obtained by using the method that lead to the utilization of compounds like Fmoc-benzylamines in the form of a compliment for the synthesis of isoindolinone with aryl groups that are deficient in electrons. This is the adaptable (versatile) and simple method which is related to different synthesis needed by drug-based medicinal and drug developments and synthesis of natural products.



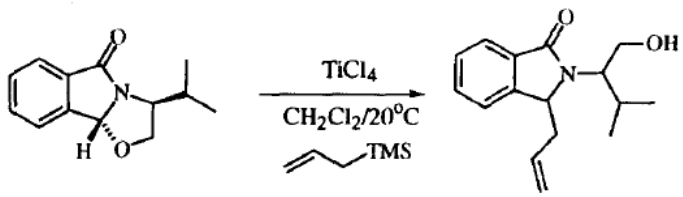
Isoindolinone derivatives are also obtained by performing direct condensation of ortho-phthaladehyde along with amino alcohol when extrinsic synthetic auxiliary is present; we have put forward a method which involves help of neighboring group by the functional group of alcohol.[29]



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.

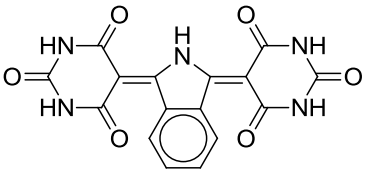


The tricyclic lactum that is derived by (+/-)-valinol was made to react with titanium tetrachloride at normal room temperature in dichloromethane before adding allyl trimethylsilane to give the required substituted isoindolinone in an isolated yield of 96%.[30-32]

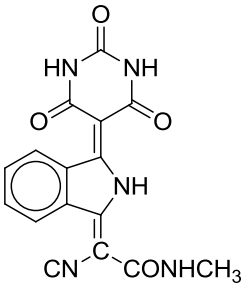


Commercially available isoindolinone and isoindolinone pigments and their applications

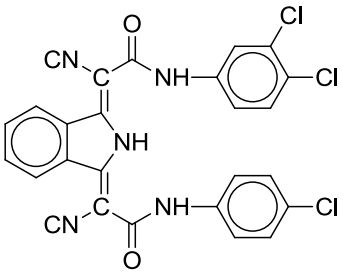
Commercially available coloring substances called pigments of isoindolinone are representatives of yellow pigment for example, pigment yellow-110, pigment yellow-139, pigment yellow-173 pigment yellow-109 and pigment yellow 185, pigment orange 66, pigment orange 61, pigment orange-69, pigment red-260, and pigment brown-38. Pigments that provides other shades have not gained so much commercial name and impact.



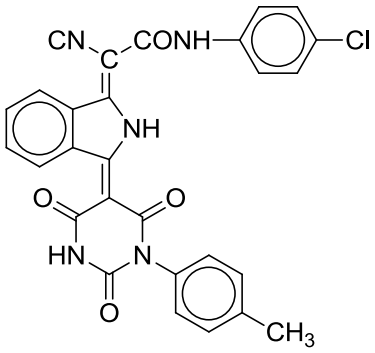
Shade - reddish yellow
Pigment yellow 139



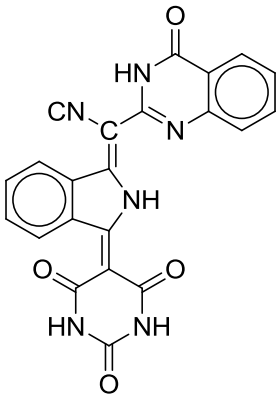
Shade - greenish yellow
Pigment yellow 185



Shade - yellowish orange
Pigment orange 66



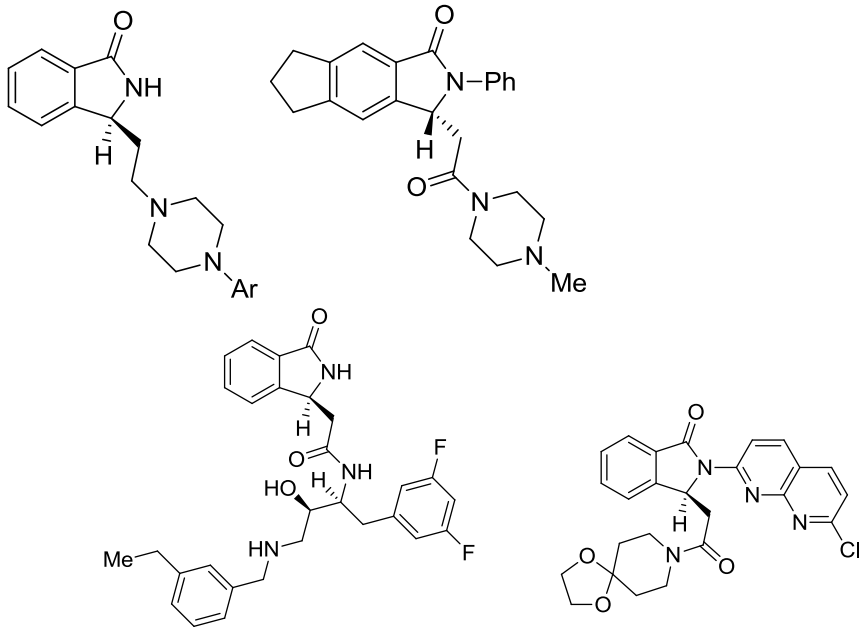
Shade - yellowish orange
Pigment orange 69



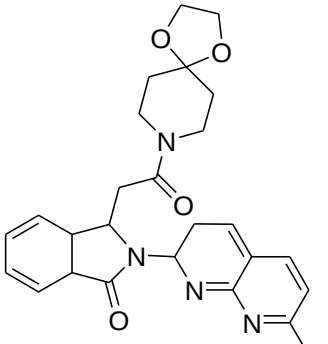
Shade - yellowish red
Pigment red 260

Biological activities of Isoindolinones

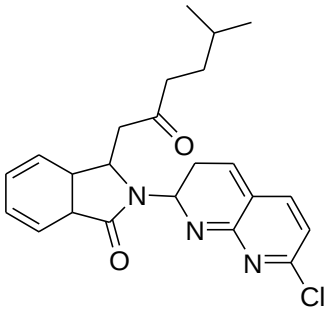
Isoindolinones are heterocyclic compounds having potential biological activities, like anti-hypertensive (high blood pressure), anti-psychotic, anti-inflammatory, and pain killer, these class of heterocyclic support also display anti-ulcer, vasodilatory, anti-viral, anti-leukemic properties.[31] These have been found to cause dose-dependent transcription in MDM2-amplified SJSA human sarcoma cell lines.



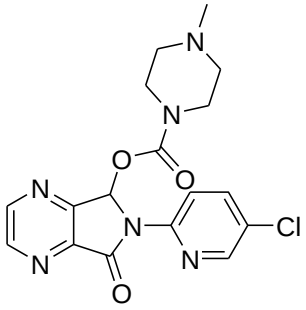
Some substituted isoindolinone possess anxiolytic hyprotics, antihypertensive, antipsychotic, antiflammatory, anaesthetic, antiulcer, vasodilatory, antiviral, antileulcemic. We can synthesise these types of substituted isoindolinone by several procedures.



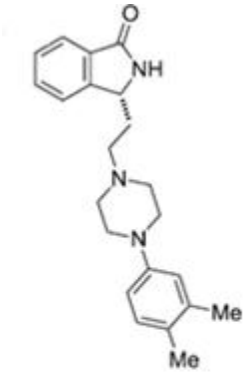
Pazinaclone



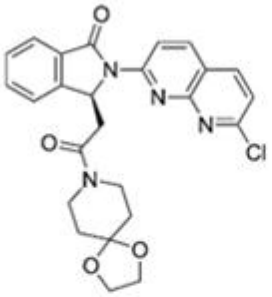
Pagoclone



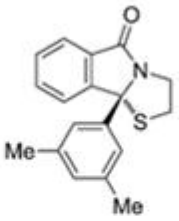
Zopiclone



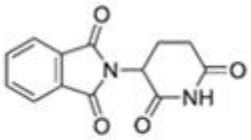
(*R*)-PD 172939
(dopamine D4 antagonist)



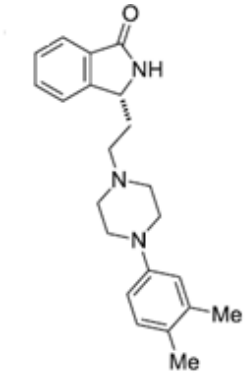
(*S*)-pazinaclone
(sedative drug)



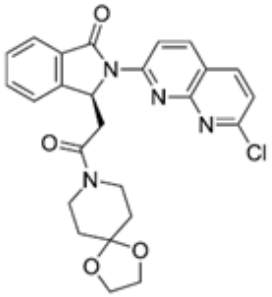
(*R*)-(+)
(antiretroviral, ARV)



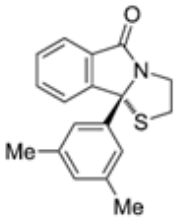
thalidomide
(teratogen)



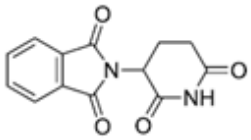
(*R*)-PD 172939
(dopamine D4 antagonist)



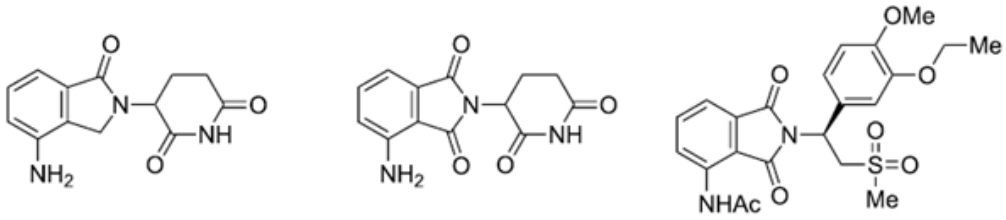
(*S*)-pazinaclone
(sedative drug)



(*R*)-(+)
(antiretroviral, ARV)



thalidomide
(teratogen)



lenalidomide (anticancer, multiple myeloma) | pomalidomide (anticancer, multiple myeloma) | apremilast (antiinflammatory)

REFERENCES

1. Luzzio, F. A.; Zacherl, D. P. Tetrahedron Lett. 1999, 40, 2087.
2. FA Luzzio; AV Mayorov; SSW Ng; EA Kruger; WD Figg. J. Med. Chem. 2003, 46: 3793.
3. M Norman; DJ Minick; GC Rigdon. J. Med. Chem. 1996, 39: 149.
4. L. Shi, L. Hu, J. Wang, X. Cao, H. Gu, Org. Lett., 2012, 14, 1876-1879.
5. Mishra, V., Bansal, K. K., Verma, A., Yadav, N., Thakur, S., Sudhakar, K., & Rosenholm, J. M. (2018),1*0*(4), 191.
6. Chaudhary, A., & Singh, S. S. (2012, September). 2012, International Conference on Computing Sciences (pp. 142-146). IEEE.
7. Mukherjee, R., 2020 Bulletin of Materials Science, *43*(1), 1-5.
8. Singh, A. (2012). Bulletin of Materials Science, *35*(6), 1031-1038.
9. K. Nozawa-Kumada, J. Kadokawa, T. Kameyama, Y. Kondo, Org. Lett., 2015, 17, 4479-4481.
10. Z.-Q. Wang, C.-G. Feng, M.-H. Xu, G.-Q. Lin, J. Am. Chem. Soc., 2007, 129, 5336-5337.
11. J. B. Campbell, R. F. Dedinas, S. Trumbower-Walsh, Synlett, 2010, 3008-3010.
12. H. S. P. Rao, A. V. B. Rao, J. Org. Chem., 2015, 80, 1506-1516.
13. W. Chen, L. Jin, Y. Zhu, X. Cao, L. Zheng, W. Mo, Synlett, 2013, 24, 1856-1860.
14. A. M. Dumas, A. J. Sieradzki, L. J. Donnelly, Org. Lett., 2016, 1848.
15. Kundu, N. G. K.; Wahab, M.; Mahanty, J. S. J. Chem. Res., Miniprint 1999, 8, 1901–1918.
16. Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. Tetrahedron1999, 55, 12361–12376.
17. Abdelkhalik, A. M.; Paul, N. K.; Jha, A. Steroids 2015, 98, 117–113.
18. Mathur, D.; Prasad, A. K.; Cameron, T. S.; Jha, A. Tetrahedron2014, 70, 5608–561.
19. Jha, A.; Naidu, A. B.; Abdelkhalik, A. M. Org. Biomol. Chem.2013, 11, 7559–7569.
20. Pericherla, K.; Kumar, A.; Jha, A. Org. Lett. 2013, 15, 4078–4081.
21. Dhanasekaran, S.; Kayet, A.; Suneja, A.; Bisai, V.; Singh, V. K.Org. Lett. 2015, 17, 2780–2783.
22. Zhang, W.; Zhou, Y.; Qian, L. Synlett 2009, 2009, 843–847.
23. Zhang, W.; Zheng, A.; Liu, Z.; Yang, L.; Liu, Z. Tetrahedron Lett.2005, 46, 5691–5694.
24. Qiao, L.; Zhou, Y.; Zhang, W. Chin. J. Chem. 2010, 28, 449–456.
25. Jha, A.; Chou, T. Y.; Al-Jaroudi, Z.; Ellis, B. D.; Cameron, T. S.Beilstein J. Org. Chem. 2014, 10, 848–857.

26. K. Hiraga and Y. Saji, PCT Int. Appl. 1984, WO 8303 410 (Chem. Abstr., 1984, 100, 51451p).
27. Sylvain Couty, Benoıˆt Liegault, Christophe Meyer and Janine Cossy, 14 November 2005
28. A. Józ´wiak et al. / Tetrahedron Letters 55 (2014) 2420–2422
29. Ordonez, M.; Tibhe, G. D.; Zamudio-Medina, A.; Viveros-Ceballos, J. L. Synthesis 2012,44,569-574
30. Sivasankaran Dhanasekaran, Vishnumaya Bisai, Rajshekhar A. Unhale, Arun Suneja,Department of Chemistry, Indian Institute of Technology Kanpur-208 016, UP, India
31. Satoshi Adachi, Masao Onozuka, Yuko Yoshida, Mitsuaki Ide, Yoko Saikawa, and Masaya Naka, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, 223-8522, Japan
32. CS Pat. 194084 (1979); CS Pat. 202940 (1981); CS Pat. 219696 (1983); CS Pat. 167097 (1976).