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BIOLOGICAL AND MEDICINAL IMPORTANCE OF 3-SUBSTITUTED, 3-HYDROXY OXINDOLES: A COMPREHENSIVE REVIEW

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Abstract: The present article includes a literature review of various naturally occurring and pharmaceutically important compounds containing 3-hydroxy oxindole framework along with their isolation and biological data. It also includes the medicinal chemistry efforts in the use of the 3-hydroxy oxindole core as a privileged scaffold in the search of novel therapeutic agents against cancer, HIV, growth disorders and other diseases.

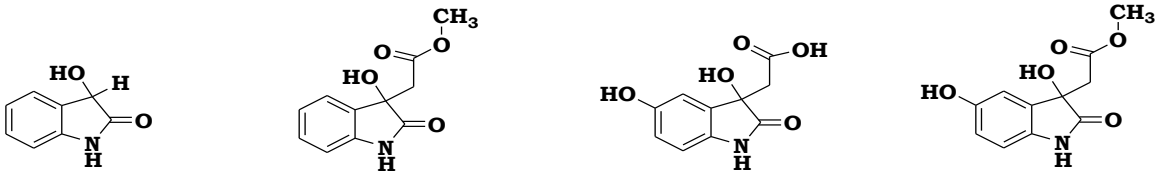
Keywords **- Oxindole; 3-Hydroxy oxindole; Biological activities, Natural Products.**

I. INTRODUCTION

Natural products contains diversely functionalized structural frameworks which possess wide varieties of biochemical properties[1] and function in a highly controlled manner.[2,3] Consequently, many natural products have explored as a promising leads for drug discovery.[4-7] Amongst the dome of natural products, 3-hydroxy oxindoles is an alkaloid class of natural product which possess unique structural diversity and biochemical properties.[8-10] Additionally, this framework is also being used as key intermediates in the complex natural product synthesis. Due to such distinct biochemical properties associated with 3-hydroxy oxindoles[11-16], it is desirable to write a review article on this framework. The current article covers the structure and bioactivity of the 3-substituted, 3-hydroxy oxindole core in natural and synthetic compounds. Section II will survey the natural products possessing 3-hydroxy oxindole core, their source and biological activities and section III will cover the medicinal chemistry efforts in the use of the 3-hydroxy oxindole core as a privileged scaffold in the search of novel therapeutic agents against cancer, HIV, growth disorders and other diseases.

II. SURVEY OF NATURAL PRODUCTS POSSESSING 3-HYDROXY OXINDOLES

The simple 3-hydroxy oxindole (**1**) is an intermediate generated by metabolic oxidation of indole. However, other metabolites (**2-4**) having similar structure framework (**Figure 1**) were derived from indole-3-acetic acid have been isolated from rice and other plants. **Sakata**[17] *et al* found that 3-hydroxy oxindole shows high radical scavenging activity.



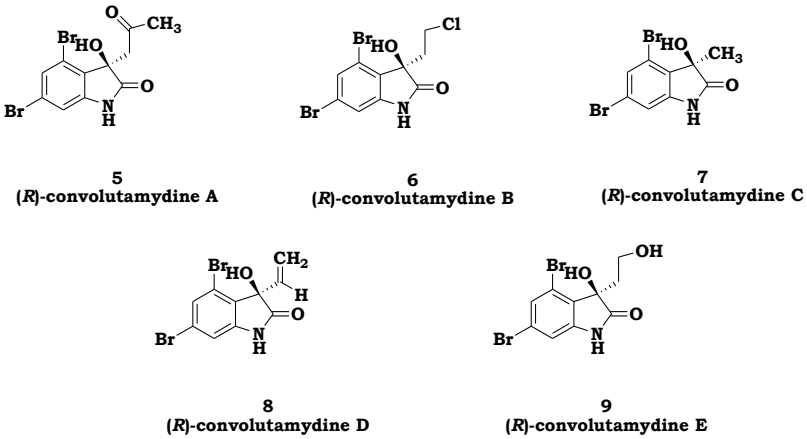
1
3-Hydroxyoxindole

2 **3** **4**

Source: Compound **1** was isolated from *Hibiscus moscheutos* L. and **2-4** were isolated from rice bran.
Bio-activity: Anti-oxidant

Figure 1: Structures of 3-hydroxy oxindoles

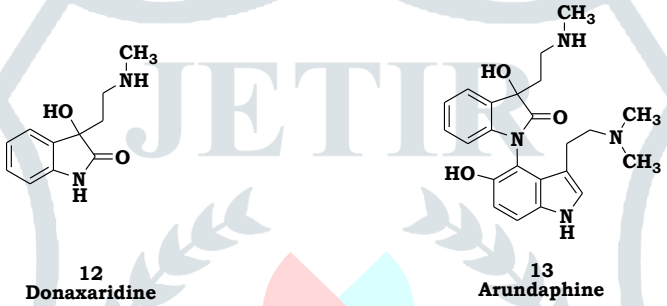
Convolutamydines A-E (**5-9**) are next members of 3-hydroxy oxindole family isolated by **Petit, Kamano**[18,19] and co-workers from a marine bryozoan Amathia convoluta collected from the northeastern Gulf of Mexico in Florida. Convolutamydines contain common 4,6-dibromo-3-hydroxy oxindole skeleton, but have different alkyl side chain at C-3 position (**Figure 2**). Convolutamydine A induces the appearance of features of normally differentiating cells in human promyelocytic leukemia cells HL-60 (12.5-25 µg/ml), such as growth arrest, adhesiveness and phagocytosis[20].



Source: *Amathia Convoluta* (maine bryozoan), Gulf of Mexico, Florida
Bio-activity: 5 Inhibits diffrentiation promyelocytic leukimia cells HL-60

Figure 2: Structures of Convolutamydines family

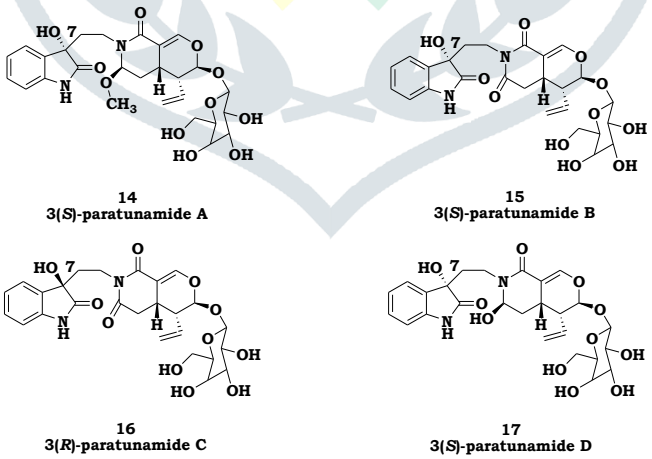
The **Khuzhaev**[22,23] *et al* have isolated dimeric alkaloid, arundaphine **13** instead of donaxiridine **12 (Figure 3**) from roots and rhizomes of giant reed *Arundo donax* L. (Poaceae).



Source: Compounds were isolated from roots and rhizomes of giant reed *Arundo donax* L. (Poaceae)
Bio-activity: Antitumor activity

Figure 3: Structures of arundaphine and donaxiridine

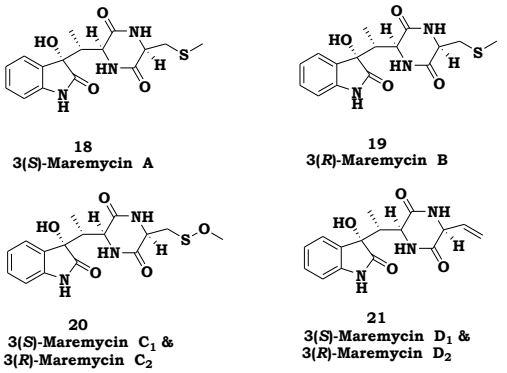
Kobayashi[24] *et al* isolated new **3-hydroxy 2-oxindoles,** namely Paratunamides A-D, **14-17** respectively (**Figure 4**) from *Cinnamodendron axillare* (Canellaceae) from Brazilian medicinal plant having local name paratude. Amongst the four Paratunamides, Paratunamide D showed moderate cytotoxicity against human epidermoid carcinoma KB cells (IC_{50} = 6 µg/mL) in vitro.



Source: Paratunamides A-D were isolated from *Cinnamodendron axillare* (Canellaceae) from Brazilian medicinal plant having local name paratude
Bio-activity: Cytotoxicity against human epidermoid carcinoma KB cells

Figure 4: Structures of Paratunamides family

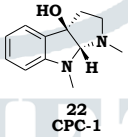
Maremycins A[25] (**18**) and Maremycins B (**19**) are diketopiperazine alkaloids class of oxindoles isolated from the culture broth of marine *Streptomyces* species B 9173 (**Figure 5**). Along with it, an inseparable 1:1 mixture of maremycins C_1 and C_2 (**20**) was obtained from *Streptomyces* sp. GT 051237, together with an inseparable 3:1 mixture of maremycins D_1 and D_2 (**21**). Maremycins B and C exhibit cytotoxicity in L-929 mouse fibroblastoma cell line, K562 human leukemia cell line and Hela cells.



Source: Compounds were isolated from Terrestrial *Streptomyces sp*. (strain GT 051237)
Bio-activity: Cytotoxicity exhibited by Maremycins B and C

Figure 5: Structures of Maremycins family

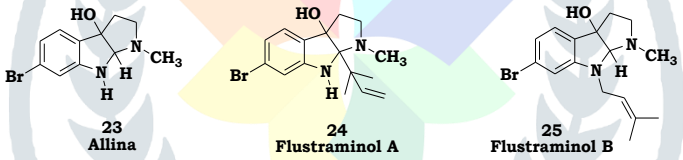
Takayama[26] and co-workers isolated a 3-hydroxy oxindole having fused polycycle pyrrolidinooxindole-type alkaloid framework named CPC-1 (**22**) from Seeds and rinds of *Chimonanthus praecox (L.) f. concolor Makino (Calycanthaceae)* **(Figure 6**). Such Pyrrolidinoindoline-type alkaloids have been known to possess antinociceptive or antibacterial activities.



Source: Isolated from *Seeds and rinds of Chimonanthus praecox (L.) f. concolor Makino (Calycanthaceae)*
Bio-activity: Antinociceptive or antibacterial activities

Figure 6: Structures of CPC-1

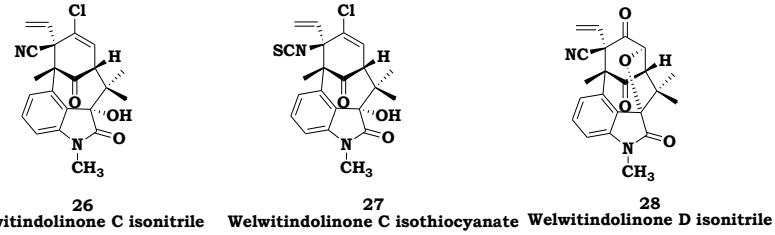
Further **Takayama** and co-workers isolated Allina (**23**) from the epigeal part of the *Allium odorum L* **(Figure 7**). In addition to this, **Christophersen**[27,28] *et al* reported the isolation and structure elucidation of brominated alkaloids Flustraminol A (**24**) and flustraminol B (**25**) from the marine bryozoan *Flustra foliacea* (L.)



Source: Compounds were isolated from Alina from the epigeal part of *Allium odorum L*. & flustraminols from the marine bryozoan *Flustra foliacea (L.)*
Bio-activity: Antinociceptive or antibacterial activities

Figure 7: Structures of Allina and flustraminols

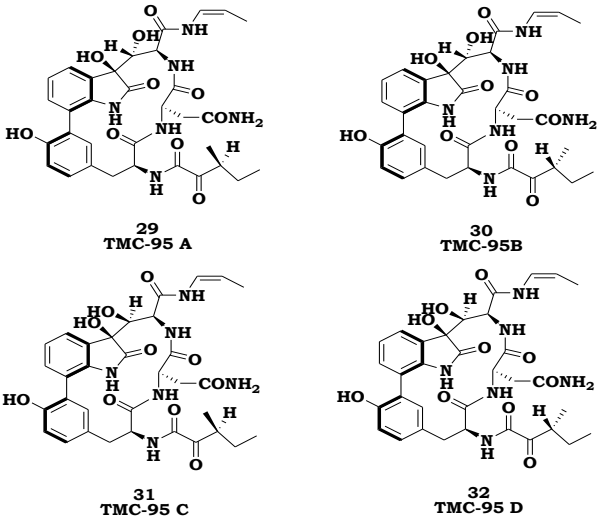
Moore[29] and co-workers isolated welwitindolinone C isonitrile (**26**), welwitindolinone C isothiocyanate (**27**) and welwitindolinone D isonitrile (**28**) from terrestrial *Fischerella muscicola* and *Fischerella major* (*Stigonemataceae*), terrestrial cyanophytes (algae) (**Figure 8**). Welwitindolinone C isothiocyanate[30] (**27**) is known to attenuate the resistance of MCF-7/ADR cells without affecting the cytotoxicity of cisplatin at doses as low as 0.1 μM.



Source: Compounds were isolated from *Fischerella muscicola* & *Fischerella major* (*Stigonemataceae*), terrestrial cyanophytes
Bio-activity: Inhibits drug resistance of MCF 7/ADR cells

Figure 8: Structures of Welwitindolinone family

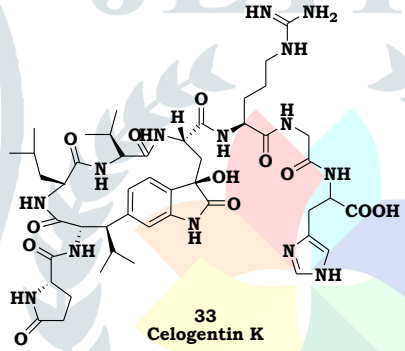
Ohnuki[31] and co-workers discovered four new diversely functionalized oxindoles named TMC-95 A-D (**29-32**) respectively (**Figure 9**). These compounds were obtained from the fermentation broth of *Apiospora montagnei* Sacc. TC 1093, isolated from a soil sample in a bamboo forest in Kanagawa, Japan. TMC-95 A-D are novel cyclic peptides containing Ltyrosine, L-aspargine, 3-hydroxy-2-indolinone, (*Z*)-1-propenylamine, and 3-methyl-2 oxopentanoic acid units which possesses proteasome inhibition activity.



Source: Fermentation broth of Apiospora montagnei Sacc.TC 1093, isolated from a soil sample in a bamboo forest in Kanagawa, Japan.
Bio-activity: Potent inhibitors of 20S proteasome TMC-95 A

Figure 9: Structures of TMC-95 family

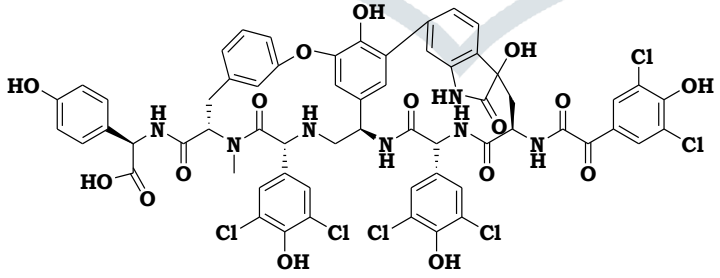
In Continuation of their work **Kobayashi**[32,33,34] *et al* isolated a new cyclic peptide with a 3-hydroxy oxindole ring named celogentin K (**33**) from the seeds of *Celosia argentea* (Amaranthaceae). Celogentin K exhibited a weak inhibitory effect on polymerization of tubulin (20% inhibition at 100 μM) as compared to that of moroidin (IC50 3.0 μM) (**Figure 10)**.



Source: Compounds were isolated from seeds of *Celosia argentea* (Amaranthaceae).
Bio-activity: Inhibits tubulin polymerization

Figure 10: Structure of Celogentin K

Similarly, **Yun**[35] and co-workers isolated neuroprotectin B (**34**) from the culture broth of Streptomyces sp. Q27107 (**Figure 11**). Neuroprotectin[36] B protected chick telenchephalic neurons from complete degeneration induced by kainate and glutamate at ED 50 of 0.24 and ~0.44 μM respectively.



Source: Compounds were isolated from *Streptomyces sp.* Q27107.
Bio-activity: Protects neuronal cells from toxicity.

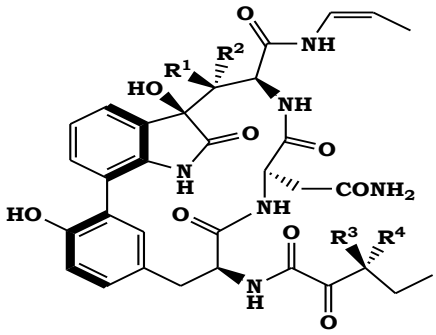
Figure 11: Structures of Neuroprotectin B

III. SURVEY OF NATURAL PRODUCTS POSSESSING 3-HYDROXY OXINDOLES

Due to prevalence and prominence of 3-hydroxy oxindoles framework, many 3-substituted, 3-hydroxy oxindoles derivatives have been used in a number of recent pharmaceutical studies. The detailed structure–activity relationship studies on 3-hydroxy oxindole framework has shown that the biological effects of these compounds are known to vary with the substituent pattern at the C3 position of oxindoles as well as the absolute configuration of the stereogenic center. Following examples will demonstrate how new structural diversity can be built into 'privileged' scaffolds to achieve either more potent or diverse biological activities.

TMC 95 (A-D) for Cancer Chemotherapy

Many excellent reviews and articles have already described the details of the SAR and medicinal chemistry of simplified TMC-95[37-50] analogs. The salient features of the TMC-95 pharmacophore (**35**) have been summarized in **Figure 12** This study shows that TMC-95 B and TMC-95 A are equipotent and the entire ketoamide side chain is replaceable with little loss in activity.



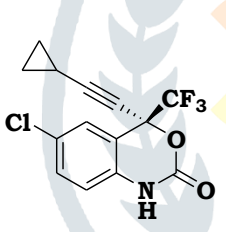
TMC-95 pharmacophore 35

TMC-95	R^1	R^2	R^3	R^4	Chymotrospin like β2	Tryspin like β2	Caspase like β1
A	H	OH	CH_3	H	0.0054	0.200	0.060
B	H	OH	H	CH_3	0.0087	0.490	0.060
C	OH	H	CH_3	H	0.3600	14.00	8.700
D	H	H	H	CH_3	0.2700	9.300	3.300

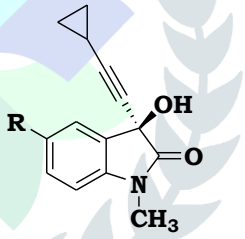
Figure 12: TMS 95 scaffold lead for rational design of inhibitors

Anti-Viral/Anti-HIV:

Boechat[51] and co-workers synthesized a series of 3-(cyclopropylethynyl)-3-hydroxy oxindoles structurally analogous to Efavirenz for their biological evaluations (**Figure 13**). Efavirenz (**36**) is a currently FDA-approved NNRTI (non-nucleoside RT inhibitor) with the best resistance profile against mutations in HIV-1 RT. Among the screened compound (**37**) showed no significant cytotoxicity and found more effective than efavirenz in inhibiting HIV-1 replication in a clinical isolate.



36
Efavirenz



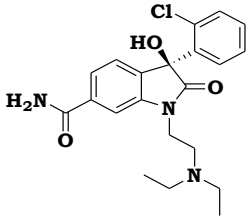
37
Designed
3-hydroxy oxindole molecule

Compound	Efavirenz	37 R = H	37 R = Br	37 R = Me
Binding energy ΔE (Kcal/mol)	-42.51	-38.26	-40.90	-40.46
Inhibit HIV1 replication IC75 (ng/ml)	450	4000	—	55

Figure 13: Comparative pharmacological properties of efavirenz

Maxi-K Channel Openers and Growth Hormone Secretagogues

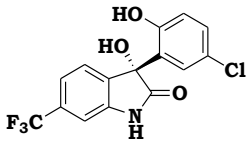
The **Taiji**[52] group at Sumitomo Pharmaceuticals, Japan screened a series of 3- hydroxyl oxindoles as GHS-receptor (GHS-R) agonists out of which compound SM-130686 (**38**) (**figure 14**) displayed potent activity (EC50 = 3 mm) and good pharmacokinetic profile in rats (bioavailability of 28 %) and was found to be a partial agonist of the GHS-R. Furthermore, oral administration of SM-130686 resulted in increased body length and fat-free body mass gain *in vivo*.



38
SM-130686

Figure 14: Structure of 3-hydroxyl oxindoles analogue SM-130686

Another 3-hydroxyl oxindoles analogue, (*R*)-3-(5-chloro-2-hydroxyphenyl)-6-(trifluoromethyl)-3-hydroxyindolin-2-one (**39**) also have been identified as potent maxi-K calcium-activated potassium (KCa) channel openers[53] (**Figure 15**). Compound (**39**) was identified as the most effective activator of maxi-K channels (outward current of 141 % *vs.* control @ 20 mM in *Xenopus laevis* oocytes). **Figure 16** Summaries the representative natural products and pharmaceutical important molecules possessing 3-hydroxy oxindole structural framework



39

Figure 15: Structure of (R)-3-(5-chloro-2-hydroxyphenyl)-6-trifluoromethyl)-3-hydroxyindolin-2-one

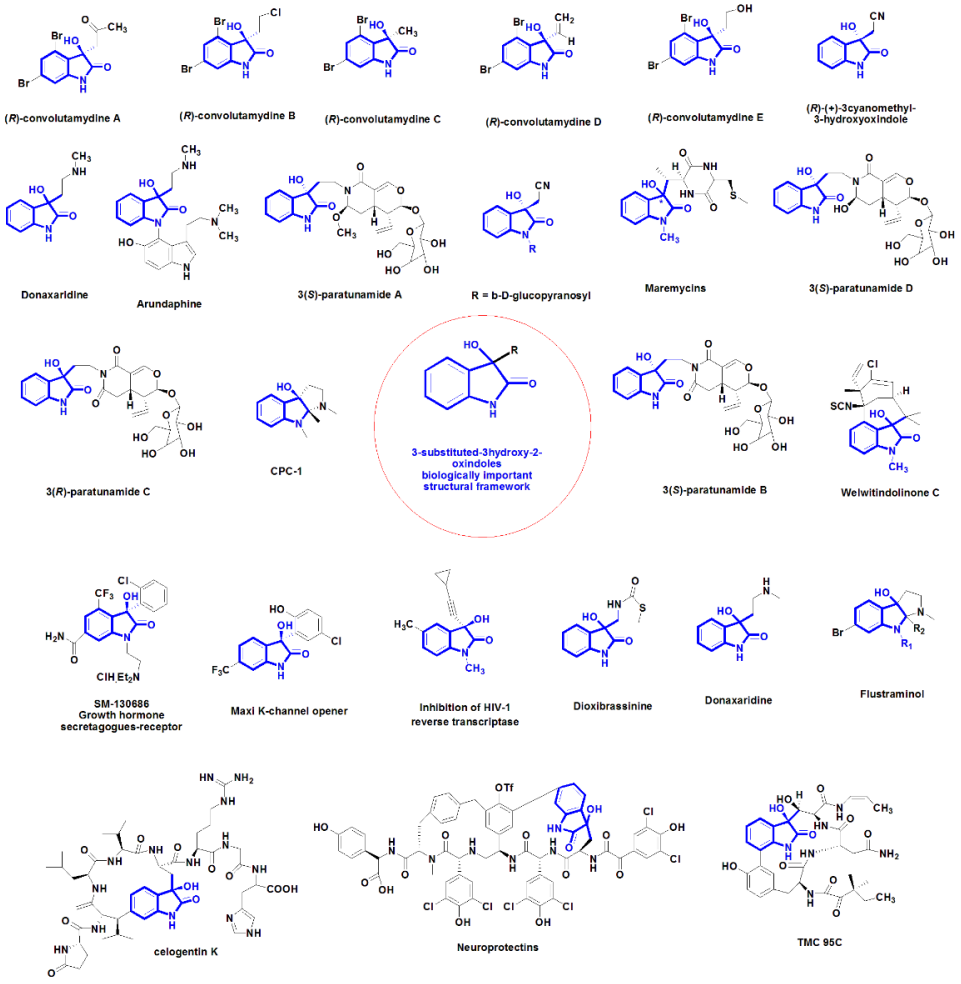


Figure 16: Summary of representative natural products and pharmaceutical important molecules possessing 3-hydroxy oxindole structural framework

III. Acknowledgment

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