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## DRUG SYNTHESIS

# SYNTHESIS AND ANTI-HIV ACTIVITY OF NOVEL 3-SUBSTITUTED PHENYL-6,7-DIMETHOXY-3a,4-DIHYDRO-3*H*-INDENO[1,2-*c*]ISOXAZOLE ANALOGUES

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**Abstract:** A series of novel 3-(substituted phenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]isoxazole analogues were synthesized by the reaction of 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanone with hydroxylamine hydrochloride. The title compounds were tested for their *in vitro* anti-HIV activity. Among the compounds, (**4g**) showed a promising anti-HIV activity in the *in vitro* testing against IIIB and ROD strains. The $IC_{50}$ of both IIIB and ROD were found to be 9.05 μM and >125 μM, respectively.

**Keywords:** isoxazoline, anti-HIV

Over the past 20 years, the human immunodeficiency virus (HIV) has emerged globally as one of the most influential infectious agents of all time. The impact of this virus can be seen in almost every facet of society, from international politics to intramural school sports. Universal precautions have become the rule, even with the most casual of human contacts. In the field of medicine, HIV and acquired immune deficiency syndrome (AIDS) caused by HIV, have introduced us to new and unusual types of disorders that has promoted an explosion of interest in the fields of infectious disease and immunology. As of late 1994, about 15 million people were infected with HIV worldwide, with greater than 1 million infected people in the United States. More than 3 million people have died of AIDS. Although an encouraging decline in the rate of new infections has occurred in certain subgroups of patients (e.g., homosexual men), the overall rate of new infections continues to increase. This trend is particularly alarming in Southeast Asia, where the seroconversion rate in intravenous drug users in Bangkok has run as high as 5% per month. In Africa, AIDS has already devastated heterosexual populations in many urban areas, and in the United States and Europe, AIDS continues to rise in intravenous drug users, their sexual partners, and their progeny. Considering that virtually all the persons infected with HIV will eventually develop AIDS, these increasing infection rates portend enormous economic burdens, societal disruption, and human suffering worldwide (1).

Human immunodeficiency virus-1 (HIV-1) infects CD4C T lymphocytes, resulting in depletion of these cells and progressive immunodeficiency. Combination antiretroviral therapy (ART) can block replication of HIV-1 and is associated with an improvement in the ability to resist opportunistic infections. However, because HIV-1 can establish a latent infection in long-lived memory CD4C T cells, current ART cannot eradicate HIV-1. As a result, life-long ART is necessary. Such therapy has several limitations, including long-term side effects and the requirement for strict adherence to the medications to prevent viral resistance. Thus, new strategies to treat HIV-1 are urgently needed (2).

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In the past decade, most heterocyclic systems have been used as a source to discover new compounds with varied biological potentials. Especially, nitrogen containing heterocyclic systems like novel pyrazolines substituted oxadiazole and substituted triazoles moieties play a vital role in discovering novel candidates having anti microbial potentials. Recently, we reported that azole derivatives possess anti-HIV antiviral activity (3, 4). From the above facts, it was evident that the microbial infections making world wide resurgence and the whole scientific community have to pave their useful hands in exploring novel entities with good therapeutic response without allowing the microbes to develop their resistance. In view of these findings and in continuation of our previous work on the synthesis of isoxazole derivatives, we report the synthesis and evaluation of anti-HIV drugs with activity against IIIB and ROD strains.

## EXPERIMENTAL

All chemicals were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene : ethyl formate : formic acid (5:4:1, v/v/v) and benzene : methanol (8:2, v/v). The spots were developed (visualized) with iodine vapors or UV light. IR spectra were recorded with Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). $^1$H-NMR spectra were recorded with Bruker AC 300 MHz spectrometer in DMSO/$CDCl_3$ using TMS as an internal standard. Mass spectra were recorded with Bruker Esquire LCMS apparatus using ESI mode and elemental analyses were recorded with Carlo Erba 1106 elemental analyzer.

### Chemistry

**General method for the preparation of 2-[(E)-1-(substituted phenyl)methylidene]-5,6-dimethoxy-1-indanone (3a-3l)** (5, 6)

5,6-Dimethoxy-1-indanone (0.01 mol) and appropriate aldehyde (0.01 mol) were dissolved in ethanol and sodium hydroxide (30%, 5 mL) with 10 mL of petrolium. ether. The reaction mixture was stirred at room temperature for 4 h. The resulting solution was allowed to stand overnight, then was poured into ice-cold water followed by neutralization with HCl. The solid separated was filtered, dried and crystallized from ethanol.

**General method for the preparation of 3-(3-substituted phenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]isoxazole (4a-4l)**

To 2-[(E)-1-(substituted phenyl)methylidene]-5,6-dimethoxy-1-indanone (**3a-3l**) (0.001 mole) in 15 mL of glacial acetic acid, 0.002 mol of hydroxylamine hydrochloride was added and the reaction mixture was refluxed for 15 h and cooled. An excess of solvent was distilled off under reduced pressure and the reaction mixture was cooled and poured onto crushed ice (20 g). The product obtained was filtered, washed with water and recrystallized from methanol.

3-(4-Methoxyphenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4a**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1550 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (2H, m, $CH_2$), 3.82 (6H,s,$OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.3 (m, 6H, arom.). MS (m/z): 326 ($M^+$ +1). Analysis: calcd. (found): C 70.14, (70.12), H 5.89, (5.87), N 4.30, (4.32)%.

3-(4-Chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4b**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1550 (C=N), 786 (C-Cl). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.4 (m, 6H, arom.). MS (m/z): 330 ($M^+$). Analysis: calcd. (found): C 65.56, (65.58), H 4.89, (4.87), N 4.25, (4.26)%.

3-(4-Dimethylaminophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4c**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1556 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 2.82 (s, 6H, $NCH_3$), 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.0 (m, 6H, arom.). MS (m/z): 339 ($M^+$ +1). Analysis: calcd. (found): C 70.99, (70.98), H 6.55, (6.53), N 8.28, (8.26)%.

6,7-Dimethoxy-3-phenyl-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4d**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1554 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.6 (m, 7H, arom.). MS (m/z): 296 ($M^+$ +1). Analysis: calcd. (found): C 73.20, (73.22), H 5.80, (5.78), N 4.74, (4.76)%.

3-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4e**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1552 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82, 3.85 (s, 12H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.0 (m, 5H, arom.). MS (m/z): 356 ($M^+$ +1). Analysis: calcd. (found): C 67.59, (67.57), H 5.96, (5.97), N 3.94, (3.96)%.

3-(3,4,5-Trimethoxyphenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4f**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1554 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82, 3.86 (s, 15H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.0 (m, 4H, arom.). MS (m/z): 386 ($M^+$ +1). Analysis: calcd. (found): C 65.44, (65.42) ,H 6.01, (6.00), N 3.63, (3.61)%.

3-(4-Flurophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4g**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1548 (C=N), 776 (C-F). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.2 (m, 6H, arom.). MS (m/z): 314($M^+$ +1). Analysis: calcd. (found): C 69.00, (69.02), H 5.15, (5.13), N 4.47, (4.46)%.

3-(2-Chlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4h**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1550 (C=N), 786 (C-Cl). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.4 (m, 6H, arom.). MS (m/z): 330($M^+$ +1). Analysis: calcd. (found): C 65.56, (65.58), H 4.89, (4.87), N 4.25, (4.26)%.

3-(2,6-Dichlorophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4i**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1556 (C=N), 786 (C-Cl). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.5 (m, 5H, arom.). MS (m/z): 365 ($M^+$ +1). Analysis: calcd. (found): C 59.36, (59.34), H 4.15, (4.16), N 3.85, (3.83)%.

3-(4-Nitrophenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4j**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1546 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.7 (m, 6H, arom.). MS (m/z): 341 ($M^+$ +1). Analysis: calcd. (found): C 63.53, (63.51), H 4.74, (4.76), N 8.23, (8.26)%.

3-(2-Furyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-c]isoxazole (**4k**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1554 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.4 (m, 2H, arom.), 7.2–7.8 (m, 3H, furyl). MS (m/z): 286 ($M^+$ +1). Analysis: calcd. (found): C 67.36, (67.35), H 5.30, (5.28), N 4.91, (4.90)%.

6,7-Dimethoxy-3-(2-thienyl)-3a,4-dihydro-3H-indeno[1,2-c]isoxazole (**4l**)

IR (KBr, $cm^{-1}$): 3042 (CH), 1573 (N-O), 1550 (C=N). $^1$H-NMR (DMSO-$d_6$, δ, ppm): 3.0–3.2 (m, 2H, $CH_2$), 3.82 (s, 6H, $OCH_3$), 3.97–4.0 (m, 1H, CH), 5.16–5.18 (d, 1H, CH), 6.6–7.0 (m, 2H, arom.), 7.2–7.5 (m, 3H, thiophenyl). MS (m/z): 302 ($M^+$ +1). Analysis: calcd. (found): C 63.77, (63.75), H 5.02, (5.00), N 4.65, (4.66)%.

## Biological Evaluation

### Microbiology

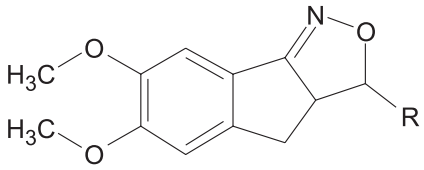
*Sample preparation:* Test compounds were dissolved in DMSO at an initial concentration of 200 μM and then were serially diluted in culture medium.

*Cell culture:* MT-4 cells (grown in RPMI 1640 containing 10% fetal calf serum (FCS), 100 UI/mL penicillin G and 100 μg/mL streptomycin) were used for cytotoxicity and anti-HIV assays. Cell cultures were checked periodically for the absence of mycoplasma contamination with a MycoTect Kit (Gibco).

### Cytotoxicity and anti-HIV assay

Activity against the HIV-I (IIIB strain) and HIV-II (ROD strain) were obtained from supernatants of persistently infected H9/IIIB cells. Multiplication in acutely infected cells was based on inhibition of virus-induced cytopathogenicity in MT-4 cells. Briefly, 50 μL of RPMI 10% FCS containing $1\times10^4$ cells were added to each well of flat-bottomed microtiter trays containing 50 μL of medium and serial dilutions of test compounds. Twenty microliters of an HIV-I/HIV-II suspension containing 100 CCID50 were then added. After a 4-day incubation at 37°C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylte-

Table 1. Physical constants of the synthesized compounds.



**4a-l**

| Compd. | R | M. p. (°C)* | Rf value* |
|---|---|---|---|
| **4a** | 4-Methoxyphenyl- | 120–122 (a) | 0.95 |
| **4b** | 4-Chlorophenyl- | 166–168 (a) | 0.90 |
| **4c** | 4-Dimethylaminophenyl- | 112–114 (b) | 0.81 |
| **4d** | Phenyl- | 136–138 (b) | 0.73 |
| **4e** | 3,4-Dimethoxyphenyl- | 117–119 (a) | 0.76 |
| **4f** | 3,4,5-Trimethoxyphenyl- | 92–94 (b) | 0.83 |
| **4g** | 4-Fluorophenyl- | 118–120 (a) | 0.75 |
| **4h** | 2-Chlorophenyl- | 139–141 (b) | 0.85 |
| **4i** | 2,6-Dichlorophenyl- | 180–182 (a) | 0.79 |
| **4j** | 3-Nitrophenyl- | 166–168 (b) | 0.90 |
| **4k** | Furyl- | 158–160 (a) | 0.88 |
| **4l** | Thienyl- | 208–210 (b) | 0.74 |

* after recrystallization from a = ethanol, b = petroleum ether. ** for toluene : ethyl formate : formic acid (5:4:1, v/v/v) mobile phase.

trazolium bromide (MTT) method. Cytotoxicity of compounds was based on the viability of mock infected cells as monitored by the MTT method (7).

## RESULTS AND DISCUSSION

### Chemistry

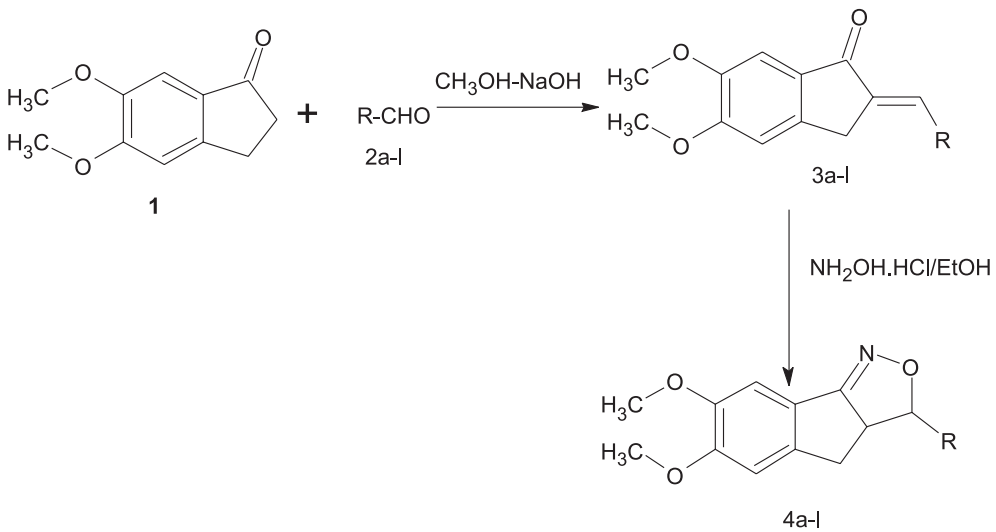
3-(3-Substituted phenyl)-6,7-dimethoxy-3a,4-dihydro-3*H*-indeno[1,2-*c*]isoxazole analogues **4a-l** described in this study are presented in Table 1, and a reaction sequence for the preparation is outlined in Scheme 1. In the initial step, 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanones were synthesized by condensing 5,6-dimethoxy-1-indanone with appropriate aromatic aldehydes in diluted methanolic sodium hydroxide solution at room temperature, then 5,6-dimethoxy-2-[(*E*)-1-phenylmethylidene]-1-indanone was treated with hydroxylamine hydrochloride in glacial acetic acid to get title compounds in 62–84% yield after recrystalization from ethanol. The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data ($^1$H-NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. In general, infra red spectra (IR) revealed CH and C-Cl peak at 1646 and 766 $cm^{-1}$, respectively. In the nuclear magnetic resonance spectra ($^1$H-NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed a doublet at δ 3.10–3.12 ppm corresponding to $CH_2$ group, singlet at δ 3.82, 3.83, 3.86 ppm corresponding to $OCH_3$, multiplet at δ 4.06–4.09 ppm corresponding to indenyl CH group, doublet at δ 5.42–5.43 ppm corresponding to isoxazole CH group and multiplet at δ 6.20–7.50 ppm corresponding to aromatic protons. The elemental analysis results were within ± 0.4% of the theoretical values.

### Anti-HIV activity

The synthesized compounds (4**a-l**) were tested for their inhibitory effect on the replication on HIV-I and HIV-II in MT-4 cell line. The results are summarized in Table 2 in comparison with standard drug nevirapine. Among the 15 compounds, compound (**4g**) was found to be the most active against replication of HIV-I and HIV-II with $IC_{50}$ of 9.05 μM (IIIB) and >125 μM (ROD). The selectivity index ($SI = CC_{50}/IC_{50}$) was found to be more than 10 with maximum protection of both IIIB, ROD up to 112–142% in two independent experiments. When

compared to reference standard – nevirapine ($IC_{50}$ 0.1 μM), most of the synthesized compounds were shown to be less active and inhibitory protection was 2–24% with a SI of >1 below their toxicity threshold. The loss of activity might be due to degeneration/rapid metabolism in the culture condition used in the screening procedure. Cytotoxicity for uninfected host cells was determined under the same conditions as antiviral activity i.e., microscopic evaluation of cell morphology of confluent cell monolayer which had (or had not) been inoculated with virus. As criterion of specific antiviral activity was taken the inhibition of virus induced cytopathogenicity at a concentration that was at least 5-fold lower than the concentration required to alter the morphology of uninfected host cells.

Among the newer derivatives, compound **(4g)** showed a promising anti-HIV activity *in vitro*




Scheme 1.

Table 2. Anti-HIV activities of the synthesized compounds

| Compd. | $III_B$ strain | | | ROD strain | | |
|---|---|---|---|---|---|---|
| | $IC_{50}$ [a] (μM) | $CC_{50}$ [b] (μM) | Protection % $IC_{50}$ [a] | $IC_{50}$ [a] (μM) | $CC_{50}$ [b] (μM) | Protection % $IC_{50}$ [a] |
| **4a** | >12.5 | 125 | 24 | >125 | 125 | 13 |
| **4b** | >12.10 | 36.1 | 12 | >1.36 | 1.36 | 10 |
| **4c** | 4.28 | 4.28 | 102 | 7.0 | 72.2 | 23 |
| **4d** | >12.90 | 12.90 | 13 | >10.76 | 10.76 | 08 |
| **4e** | >11.73 | 11.73 | 24 | >11.81 | 1.25 | 24 |
| **4f** | >13.47 | 13.47 | 22 | >66.20 | 66.20 | 23 |
| **4g** | 9.05 | >125 | 142 | 63.55 | >125 | 112 |
| **4h** | >67.97 | 67.97 | 08 | >11.54 | 11.54 | 17 |
| **4i** | >53.20 | 53.20 | 24 | >53.20 | 53.20 | 20 |
| **4j** | >13.83 | 13.83 | 14 | >13.83 | 13.83 | 12 |
| **4k** | >10.97 | 10.76 | 10 | >10.97 | 10.76 | 17 |
| **4l** | >11.73 | 11.73 | 03 | >31.02 | 31.02 | 14 |
| **Nev.** | 0.05 | >4 | 123 | >4 | >4 | 0 |

[a]Required to cause a microscopically detecable alteration of normal cell morphology.
[b]Required to reduce virus-induced cytopathogenicity by 50%. Nev. = nevirapine.

against used IIIB strains. It is conceived that derivatives showing anti-HIV activity can be further modified to exhibit better anti-HIV chemotherapeutic potential. Further studies to acquire more information about quantitative structure-activity relationships (QSAR) are in progress in our laboratory.

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