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# SYNTHESIS OF SOME HETEROCYCLE CONTAINING UREA DERIVATIVES AND THEIR ANTI-VIRAL ACTIVITY

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**Abstract-** Some new isoindol heterocyclic ureas (**6a-6i**) have been synthesized using *N*-aminophthalimide (**2**) and ethyl *N*-monosubstituted/ethyl *N,N*-disubstituted carbamate (**5a-5i**). All the newly synthesized final compounds have been evaluated for their anti-viral activities against a variety of viruses. The compound (**6f**) with the methoxy substituent showed reasonably better activity as compared to the standard drugs against all the viruses (*cf*. Tables 1, 2 and 3). Further, all the products (**6a-6i**) were found to be active against Vesicular stomatitis virus, Coxsackie virus B4 and Respiratory syncytical virus (*cf*. Table 2) and the compounds (**6h**) and (**6i**) displayed better antiviral activity in comparison to Brivudin and (S)-DHPA (*cf*. Table 3).

## INTRODUCTION

The urea functionality manifests neuroprotective activity and is also a key structural element of many biologically active substrates, such as enzyme inhibitors and peptidomimetics.[1-5] Urea derivatives possess biological activities such as anti-bacterial, anti-fungal, anti-neoplastic, hypocholesterolemic, anti-ulcer, gastric protective activities, anti-acetylcholinesterase, anti-diabetic, anti-arrhythmic, hypo- and hypertensive, and plant growth regulating activities.[6-9] Recently, cyclic ureas have gained importance as HIV-1 protease inhibitors which are important components of many highly active anti-retroviral therapy regimens.[10-19] Urea undergoes a variety of chemical reactions to afford wide range of important compounds.[20-30] In addition, they have also been used as chiral auxiliaries for asymmetric synthesis.[31]

Due to their broad spectrum applications, the synthesis of urea derivatives has received considerable attention.[32-41] Extensive investigations have recently been carried out for the preparation of libraries of urea compounds with potential biological activities.[42-47] Mono- or *N,N*-disubstituted urea derivatives have been prepared as follows:

(i). By the reaction of unsubstituted urea with alkylamines or their hydrochloride salts and subsequent loss of ammonia or ammonium halide, to yield the expected substituted ureas.[48]

(ii). By the aminolysis of isonitriles or cyanamides.[49,50]

(iii). By the conversion of nitrourea into substituted urea by the action of amines.[51]

(iv). By the reaction of alkali metal cyanates with amines.[52]

(v). By the reductive alkylation, whereby the substituents may be introduced into urea.[53]

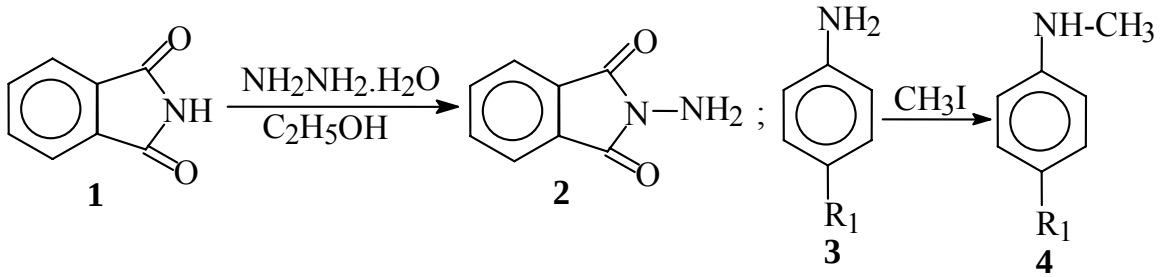
Many of the above mentioned synthetic methodologies described for the preparation of ureas suffer from drawbacks, such as long reaction times, harsh reaction conditions, low product yields, occurrence of side products and lack of versatility. Further, some of the reagents employed are expensive and toxic. In view of the above, we report herein a convenient method for the preparation of some novel heterocyclic ureas employing *N*-aminophthalimide and ethyl *N*-monosubstituted/ethyl *N*,*N*-disubstituted carbamate.

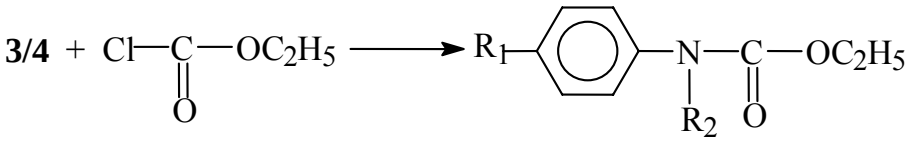
## RESULTS AND DISCUSSION

A facile synthesis of 1-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-substituted phenyl)ureas (**6a-f)** and 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1-(4-substituted phenyl)-1-methylureas (**6g-i)** has been achieved adopting the steps described in Scheme 1. Phthalimide (**1**) was initially allowed to react with hydrazine hydrate (96%) in ethanol to afford *N*-aminophthalimide (**2**). Refluxing a mixture of *p*-substituted aniline (**3**) and methyl iodide in solvent methanol provided *N*-methyl *p*-substituted aniline (**4**). Equimolar reaction of **3/4** with ethyl chloroformate in solvent ether furnished ethyl *p*-substituted phenylcarbamate (**5a-f)** or ethyl *N*-*p*-substituted phenyl, *N*-methylcarbamate (**5g-i)** in reasonably good yield. The condensation of *N*-aminophthalimide (**2**) with the substrates (**5a-f)** and (**5g-i)** was finally carried out to obtain the product 1-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-(4-substituted phenyl)-urea / 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1-(4-substituted phenyl)-1-methylurea (**6**). The products (**6a-i)** were recrystallized using ethanol/benzene and were fully characterized based on their mp, elemental analysis and spectral data.

All the isoindol urea derivatives (**6a-i)** were subsequently subjected to their *in vitro* anti-viral screening against a number of viruses and the results were compared with standard drugs (Tables 1, 2 and 3). Cytotoxicity and anti-viral activity of the compounds have been performed in HEL, HeLa and Vero cell cultures. The anti-viral activity has been expressed in terms of minimum inhibitory concentration (μg/mL) which is the least concentration required to reduce cytopathogenicity by 50%. These compounds have also been evaluated for their minimum cytotoxic concentration (μg/mL) which is required to cause a microscopically detectable alteration of normal cell morphology.

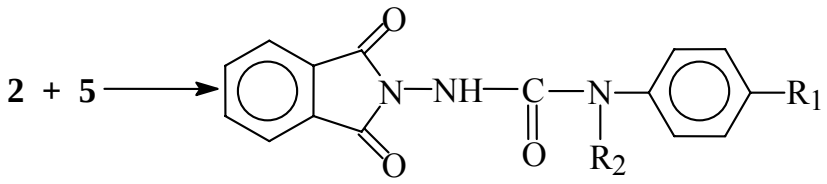
As an outcome, the compounds (**6d**, **6f** and **6g**) are found to be more active than the standard drug Ribavirin against Herpes simplex virus-1(KOS), Herpes simplex virus-2 (G), Vesicular stomatitis virus and Herpes simplex virus-1 $TK^{-1}$ KOS $ACV^{r}$.




**3** : $R_1$ = F, Cl, Br, $NO_2$, COOH, $OCH_3$
$R_2$ = H
**4** : $R_1$ = Cl, Br, $NO_2$ ; $R_2$ = $CH_3$

**5a** : $R_1$ = F, $R_2$ = H ; **5b** : $R_1$ = Cl , $R_2$ = H
**5c** : $R_1$ = Br, $R_2$ = H ;**5d** : $R_1$ = $NO_2$, $R_2$ = H
**5e** : $R_1$ = COOH, $R_2$ = H ;**5f** : $R_1$ = $OCH_3$, $R_2$ = H
**5g** : $R_1$ = Cl, $R_2$ = $CH_3$ ; **5h** : $R_1$ = Br, $R_2$ = $CH_3$
**5i** : $R_1$ = $NO_2$, $R_2$ = $CH_3$




**6a** : $R_1$ = F, $R_2$ = H ; **6b** : $R_1$ = Cl, $R_2$ = H
**6c** : $R_1$ = Br, $R_2$ = H ; **6d** : $R_1$ = $NO_2$ $R_2$ = H
**6e** : $R_1$ = COOH, $R_2$ = H ; **6f** : $R_1$ = $OCH_3$, $R_2$ = H
**6g**: $R_1$ = Cl, $R_2$ = $CH_3$ ; **6h** : $R_1$ = Br, $R_2$ = $CH_3$
**6i** : $R_1$ = $NO_2$, $R_2$ = $CH_3$

**Scheme 1**

Compound (**6d**) shows lesser activity than Ribavirin against Vaccinia virus, whereas compound (**6f**) and (**6g**) are comparable to Ribavirin against Vaccinia virus (*cf.* Table 1). The compounds (**6d**, **6f** and **6g**) have better activities than Brivudin against Vesicular stomatitis virus and Herpes simplex virus-1 $TK^{-1}$ KOS $ACV^r$. The compounds (**6a-c**, **6e**, **6h** and **6i**) and Brivudin show equal activities against Vesicular stomatitis virus and Herpes simplex virus-1 $TK^{-1}$ KOS $ACV^r$. Compounds (**6d, 6f** and **6g)** are more active than Acyclovir against Vaccinia virus and Vesicular stomatitis virus. Compounds (**6f**) and (**6g**) show better activity than Ganciclovir against Vaccinia virus, while the compounds (**6d**, **6f** and **6g)** are better than Ganciclovir against Vesicular stomatitis virus.

**Table-1:** Cytotoxicity and anti-viral activity of the compounds (**6a-i**) in HEL cell cultures

| Compound | Minimum Cytotoxic Concentration[1] (μg/mL) | Minimum Inhibitory Concentration[2] (μg/mL) | | | | |
|---|---|---|---|---|---|---|
| | | Herpes simplex virus-1 (KOS) | Herpes simplex virus-2 (G) | Vaccinia virus | Vesicular stomatitis virus | Herpes simplex virus-1 $TK^-$KOS $ACV^r$ |
| **6a** | >400 | >400 | >400 | >400 | >400 | >400 |
| **6b** | >400 | >400 | >400 | >400 | >400 | >400 |
| **6c** | >400 | >400 | >400 | >400 | >400 | >400 |
| **6d** | 400 | >80 | >80 | 240 | >80 | >80 |
| **6e** | >400 | >400 | >400 | >400 | >400 | >400 |
| **6f** | 400 | >80 | >80 | >80 | >80 | >80 |
| **6g** | 400 | >80 | >80 | >80 | >80 | >80 |
| **6h** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6I** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| Brivudin | ≥400 | 0.0768 | 80 | 48 | >400 | >400 |
| Ribavirin | >400 | >400 | 240 | 80 | 240 | 240 |
| Acyclovir | >400 | 0.384 | 0.384 | >400 | >400 | 9.6 |
| Ganciclovir | >100 | 0.0064 | 0.096 | >100 | >100 | 0.48 |

[1]Required to cause a microscopically detectable alteration of normal cell morphology.

[2]Required to reduce virus-induced cytopathogenicity by 50%.

**Table-2:** Cytotoxicity and anti-viral activity of the compounds (**6a-i**) in HeLa cell cultures

| Compound | Minimum Cytotoxic Concentration[1] (μg/mL) | Minimum Inhibitory Concentration[2] (μg/mL) | | |
|---|---|---|---|---|
| | | Vesicular stomatitis virus | Coxsackie virus B4 | Respiratory syncytical virus |
| **6a** | 400 | >80 | >80 | >80 |
| **6b** | 400 | >80 | >80 | >80 |
| **6c** | 400 | >80 | >80 | >80 |
| **6d** | 80 | >16 | >16 | >16 |
| **6e** | 400 | >80 | >80 | >80 |
| **6f** | 80 | >16 | >16 | >16 |
| **6g** | 400 | 80 | 80 | 80 |
| **6h** | ≥80 | >80 | >80 | >80 |
| **6i** | 400 | >80 | >80 | >80 |
| Brivudin | ≥400 | >400 | >400 | >400 |
| (S)-DHPA | >400 | >400 | >400 | >400 |
| Ribavirin | ≥400 | 48 | 48 | 16 |

[1]Required to cause a microscopically detectable alteration of normal cell morphology.

[2]Required to reduce virus-induced cytopathogenicity by 50%.

A perusal of Table 2 indicates that all the compounds (**6a-i)** are more active (lesser MIC) than standard drugs Brivudin and (S)-DHPA against Vesicular stomatitis virus, Coxsackie virus B4 and Respiratory synctial virus. The compounds (**6d**) and (**6f**) are even better than Ribavirin against Vesicular stomatitis virus and Coxsackie virus B4.

**Table-3:** Cytotoxicity and anti-viral activity of compounds (**6a-i**) in Vero cell cultures

| Compound | Minimum Cytotoxic Concentration[1] (μg/mL) | Minimum Inhibitory Concentration[2] (μg/mL) | | | | |
|---|---|---|---|---|---|---|
| | | Parainf-luenza-3 virus | Reovirus-1 | Sindbis virus | Coxsackie virus B4 | Punta Toro virus |
| **6a** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6b** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6c** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6d** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6e** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6f** | 400 | >80 | >80 | >80 | >80 | >80 |
| **6g** | ≥400 | >400 | >400 | >400 | >400 | >400 |
| **6h** | 400 | >80 | >80 | >80 | >80 | >80 |
| **6i** | 400 | >80 | >80 | >80 | >80 | >80 |
| Brivudin | >400 | >400 | >400 | >400 | >400 | >400 |
| (S)-DHPA | >400 | >400 | >400 | >400 | >400 | >400 |
| Ribavirin | >400 | 48 | 48 | 240 | >400 | 48 |

[1]Required to cause a microscopically detectable alteration of normal cell morphology.
[2]Required to reduce virus-induced cytopathogenicity by 50%.

It is evident from Table 3 that the compounds (**6f**, **6h** and **6i**) have better anti-viral activity than Brivudin and (S)-DHPA against Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus. The compounds (**6f**, **6h** and **6i**) are found to be more active than Ribavirin against Sindbis virus and Coxsackie virus B4. Thus, the synthesized compounds (**6a-i**) are found to possess potential anti-viral activity against a number of viruses and the compound (**6f**) has been concluded to be the most promising compound possessing a broad spectrum of anti-viral activity.

## EXPERIMENTAL

The melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL FT-NMR spectrometer FX-90Q and the chemical shifts are expressed as δ/ppm, downfield to TMS as internal reference.

### Synthesis of *N*-aminophthalimide (2)[54]

96% Hydrazine hydrate (4.1 mL, 0.081 mol), ethyl alcohol (80 mL) and powdered phthalimide (**1**, 11.9 g,

0.081 mol) were placed in a round bottom flask fitted with a reflux condenser. The mixture was then shaken for 2 min at rt and the resulting spongy mass was quickly heated and refluxed for 3 min. Water (50 mL) was then quickly added to it and the clear solution obtained was poured into a large volume of water (200 mL). The resulting *N*-aminophthalimide (**2**) was filtered, dried and recrystallised from ethyl alcohol. The aqueous filtrate on acidification also gave **2** which was recrystallised.

Yield 5.8 g (44.2%); mp 200-203°C (lit.,[54] 200-205°C); IR $cm^{-1}$ (KBr) 3390, 1775, 1752, 1606, 1388, 1309, 1052, 718, 536; $^1$H-NMR (DMSO-$d_6$), δ/ppm: 5.0 (s, 2H, $NH_2$), 7.7-8.1 (m, 4H, ArH).

**Preparation of *N*-methyl *p*-substituted aniline (4)**[55]

A mixture of *p*-substituted aniline (**3**, 0.025 mol) and MeI (0.6 mL, 0.01 mol) was refluxed in methanol (25 mL) for 10 h. The reaction mixture was cooled and made alkaline by adding 20% KOH. A solution of $ZnCl_2$ (1.50 g, 0.011 mol) in $H_2O$ (1.5 mL) was added. The mixture was cooled to 5°C, stirred and filtered at the suction pump. The thick paste was extracted several times with petroleum ether (bp 60-80°C). The combined petroleum ether extracts were successively washed with water and 25% ammonia solution and dried over anhydrous $MgSO_4$. The solvent was removed at rotary evaporator and the residue was recrystallized with ethanol.

***N*-Methyl-*p*-chloroaniline:**

Yield 2.52 g (71.2%); bp 239°C (lit.,[56] 240°C); IR $cm^{-1}$ (neat) 3480, 2942, 1618, 1495, 1325, 1287, 1181, 1088, 822, 642, 506; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (d, *J*= 1.1 Hz, 3H, $CH_3$), 4.0 (br s, 1H, NH), 6.4 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.0 (d, *J*= 9.3 Hz, 2H, Ar-H).

***N*-Methyl-*p*-bromoaniline:**

Yield 2.03 g (43.9%); mp > 300°C; IR $cm^{-1}$ (KBr) 3455, 2941, 1611, 1593, 1488, 1472, 1373, 1288, 1180, 1068, 828, 818, 505; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (d, *J*= 1.1 Hz, 3H, $CH_3$), 4.0 (br s, 1H, NH), 6.3 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.2 (d, *J*= 9.3 Hz, 2H, Ar-H). Anal. Calcd for $C_7H_8NBr$ C, 45.18; H, 4.30; N, 7.53. Found C, 45.08; H, 4.42; N, 7.41.

***N*-Methyl-*p*-nitroaniline:**

Yield 1.58 g (41.1%); mp 150°C (lit.,[57] 152°C); IR $cm^{-1}$ (KBr) 3349, 2941, 1634, 1580, 1480, 1473, 1372, 1327, 1298, 1118, 841, 693; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (d, *J*= 1.0 Hz, 3H, $CH_3$), 4.0 (br s, 1H, NH), 6.7 (d, *J*= 9.2 Hz, 2H, Ar-H), 8.0 (d, *J*= 9.2 Hz, 2H, Ar-H)

**Preparation of ethyl *p*-substituted phenylcarbamate or ethyl *N*-*p*-substituted phenyl, *N*-methylcarbamate (5)**[58]

In a three necked round bottom flask fitted with a condenser and magnetic stirrer and cooled by an ice-salt mixture, was added ether (25 mL) and *p*-substituted aniline (**3**) **(**0.0206 mol) / *N*-methyl-*p*-substituted aniline (**4**) (0.0206 mol). The mixture was stirred continuously while maintaining the temperature below 5°C. Ethyl chloroformate (1.9 mL, 0.0206 mol) was subsequently added dropwise under 5°C. When half of the ethyl chloroformate was added to the reaction mixture, a cold aq 20% solution of equimolar NaOH

(1.2 mL, 0.0206 mol) was added gradually along with the rest of the ethyl chloroformate at such a rate so that the last portions of the two solutions were added simultaneously. After stirring for 1 h, the ether layer was separated and the aqueous phase was extracted with ether (2×20 mL). The combined ether extract was dried with $K_2CO_3$, filtered and evaporated at rotary evaporator to afford the product (**5a-i**).

**Ethyl *p*-fluorophenylcarbamate (5a):**

Yield 2.89 g (76.5%); mp 47°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3402, 2985, 1700, 1574, 1555, 1429, 1350, 1259, 1192, 1089, 1022, 799; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.8 Hz, 3H, $CH_3$), 4.1 (q, *J*= 6.8, 13.1 Hz, 2H, $CH_2$), 6.9 (d, *J*= 9.5 Hz, 2H, Ar-H), 7.6 (d, *J*= 9.5 Hz, 2H, Ar-H), 8.0 (s, 1H, NH). Anal. Calcd for $C_9H_{10}NO_2F$; C, 59.01; H, 5.46; N, 7.65. Found; C, 58.96; H, 5.55; N, 7.78.

**Ethyl *p*-chlorophenylcarbamate (5b):**

Yield 2.01 g (49.0%); mp 59°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3321, 2961, 1699, 1535, 1404, 1305, 1261, 1094, 1024, 800, 680; $^1$H-NMR (DMSO-$d_6$), δ/ppm: 1.3 (t, *J*= 6.8 Hz, 3H, $CH_3$), 4.1 (q, *J*= 6.8, 13.2 Hz, 2H, $CH_2$), 7.2 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.6 (d, *J*= 9.3 Hz, 2H, Ar-H), 8.0 (s, 1H, NH). Anal. Calcd for $C_9H_{10}NO_2Cl$; C, 54.14; H, 5.01; N, 7.01. Found; C, 54.31; H, 4.88; N, 6.93.

**Ethyl *p*-bromophenylcarbamate (5c):**

Yield 4.00 g (79.7%); mp 82°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3300, 2933, 1705, 1590, 1570, 1440, 1100, 1026, 570; $^1$H-NMR (DMSO-$d_6$), δ/ppm: 1.3 (t, *J*= 6.8 Hz, 3H, $CH_3$), 4.1 (q, *J*= 6.8, 13.2 Hz, 2H, $CH_2$), 7.4 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.5 (d, *J*= 9.3 Hz, 2H, Ar-H), 8.0 (s, 1H, NH). Anal. Calcd for $C_9H_{10}NO_2Br$; C, 44.28; H, 4.10; N, 5.74. Found; C, 44.41; H, 3.95; N, 5.88.

**Ethyl *p*-nitrophenylcarbamate (5d):**

Yield 4.27 g (97.8%); mp 127°C (Recrystallised with EtOH) (lit.,[54] 129°C); IR $cm^{-1}$ (KBr): 3379, 2990, 1739, 1599, 1551, 1514, 1416, 1333, 1265, 1219, 1109, 1059, 852, 748, 665; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.8 Hz, 3H, $CH_3$), 4.1 (q, *J*= 6.8, 13.1 Hz, 2H, $CH_2$), 7.9 (d, *J*= 9.2 Hz, 2H, Ar-H), 8.0 (s, 1H, NH), 8.1 (d, *J*= 9.2 Hz, 2H, Ar-H).

**Ethyl *p*-carboxyphenylcarbamate (5e):**

Yield 4.05 g (94.1%); mp 156°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3333, 2998, 1711, 1668, 1597, 1535, 1416, 1319, 1294, 1230, 1179, 1062, 945, 864, 841, 773; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.6 Hz, 3H, $CH_3$), 4.1 (q, *J*= 6.7, 13.2 Hz, 2H, $CH_2$), 7.8 (d, *J*= 9.2 Hz, 2H, Ar-H), 8.0 (s, 1H, NH), 8.1 (d, *J*= 9.2 Hz, 2H, Ar-H), 11.0 (s, 1H, COOH). Anal. Calcd for $C_{10}H_{11}NO_4$; C, 57.41; H, 5.26; N, 6.69. Found; C, 57.30; H, 5.41; N, 7.06.

**Ethyl *p*-methoxyphenylcarbamate (5f):**

Yield 3.47 g (86.4%); mp 53°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3319, 2839, 1701, 1601, 1537, 1442, 1415, 1315, 1238, 1186, 1074, 1028, 825, 775; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.6 Hz, 3H, $CH_3$), 3.7 (s, 3H, $OCH_3$), 4.1 (q, *J*= 6.7,13.1 Hz, 2H, $CH_2$), 6.7 (d, *J*= 8.9 Hz, 2H, Ar-H), 7.5 (d, *J*= 8.9 Hz,

2H, Ar-H), 8.0 (s, 1H, NH). Anal. Calcd for $C_{10}H_{13}NO_3$; C, 61.53; H, 6.66; N, 7.17. Found; C, 61.47; H, 6.75; N, 7.12.

**Ethyl *p*-chlorophenylmethylcarbamate (5g):**

Yield 1.37 g (31.2%); bp >250°C; IR $cm^{-1}$ (neat) 2898, 1677, 1580, 1560, 1433, 1379, 1190, 1150, 1008, 684; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*=6.6 Hz, 3H, $CH_3$), 2.8 (s, 3H, N-$CH_3$), 4.1 (q, *J*= 6.5,13.1 Hz, 2H, $CH_2$), 7.2 (d, *J*= 9.2 Hz, 2H, Ar-H), 7.6 (d, *J*= 9.2 Hz, 2H, Ar-H). Anal. Calcd for $C_{10}H_{12}NO_2Cl$; C, 56.21; H, 5.62; N, 6.55. Found; C, 56.09; H, 5.67; N, 6.68.

**Ethyl *p*-bromophenylmethylcarbamate (5h):**

Yield 3.65 g (60.7%); mp >250°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 2933, 1695, 1558, 1440, 1189, 1149, 1007, 569; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.6 Hz, 3H, $CH_3$), 2.8 (s, 3H, N-$CH_3$), 4.1 (q, *J*= 6.5, 13.1 Hz, 2H, $CH_2$), 7.4 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.5 (d, *J*= 9.3 Hz, 2H, Ar-H). Anal. Calcd for $C_{10}H_{12}NO_2Br$; C, 46.52; H, 4.65; N, 5.42. Found; C, 46.40; H, 4.71; N, 5.58.

**Ethyl *p*-nitrophenylmethylcarbamate (5i):**

Yield 1.59 g (34.2%); mp 45°C (Recrystallised with EtOH) (lit.,[59] 45°C); IR $cm^{-1}$ (KBr) 2900, 1723, 1600, 1550, 1188, 1197, 1006, 1370, 1210; $^1$H-NMR (DMSO-$d_6$), δ/ppm 1.3 (t, *J*= 6.6 Hz, 3H, $CH_3$), 2.8 (s, 3H, N-$CH_3$), 4.1 (q, *J*= 6.5, 13.1 Hz, 2H, $CH_2$), 7.9 (d, *J*= 9.2 Hz, 2H, Ar-H), 8.1 (d, *J*= 9.2 Hz, 2H, Ar-H).

**Preparation of 1-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-(4-substituted phenyl)urea and 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1-(4-substituted phenyl)-1-methylurea (6)**

Equimolar quantities of *N*-aminophthalimide (**2**) (1.14 g, 0.007 mol) and ethyl *p*-substituted phenylcarbamate / ethyl *N*-*p*-substituted phenyl, *N*-methylcarbamate (**5**) (0.007 mol) were dissolved in ethanol (30 mL). The reaction mixture was refluxed for 1-2 h. After the completion of the reaction as checked by TLC, the solvent was removed at rotary evaporator and the residue was treated twice with diethyl ether (2x20 mL). The combined ether extract was dried over anhydrous sodium sulphate and then evaporated to afford the product (**6a-i)**, which was recrystallised from ethanol/benzene and characterized.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-fluorophenyl)urea (6a):**

Yield 1.41 g (67.7%); mp >245°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3344, 3012, 1700, 1699, 1650, 1574, 1555, 1429, 1380, 800; $^1$H-NMR (DMSO-$d_6$), δ/ppm 6.9 (d, *J*= 9.4 Hz, 2H, Ar-H), 7.6 (m, 4H, Ar-H), 8.1 (d, *J*= 9.4 Hz, 2H, Ar-H), 8.3-8.5 (m, 2H, NH); Anal. Calcd for $C_{15}H_{10}N_3O_3F$; C, 60.20; H, 3.37; N, 14.04. Found; C, 60.00; H, 3.30; N, 14.00.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-chlorophenyl)urea (6b):**

Yield 1.90 g (86.2%); mp >250°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3358, 3012, 1697, 1639, 1593, 1537, 1493, 1404, 831, 771, 682; $^1$H-NMR (DMSO-$d_6$), δ/ppm 7.2 (d, *J*= 9.3 Hz, 2H, Ar-H), 7.4-7.7 (m, 4H, Ar-H), 8.1 (d, *J*= 9.4 Hz, 2H, Ar-H), 8.3-8.5 (m, 2H, NH); Anal. Calcd for $C_{15}H_{10}N_3O_3Cl$; C, 57.07; H, 3.19; N, 13.31. Found; C, 57.00; H, 3.00; N, 13.49.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-bromophenyl)urea (6c):**

Yield 1.84 g (73.1%); mp 250°C (decomp) (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3322, 3013, 1690, 1629, 1525, 1440, 802, 592; $^1$H-NMR (DMSO-$d_6$), δ/ppm 7.4-7.7 (m, 6H, Ar-H), 8.1 (d, *J*= 9.3 Hz, 2H, Ar-H), 8.3-8.5 (m, 2H, NH); Anal. Calcd for $C_{15}H_{10}N_3O_3Br$; C, 50.02; H, 2.80; N, 11.67. Found; C, 49.90; H, 2.60; N, 11.79.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-nitrophenyl)urea (6d):**

Yield 2.13 g (76.2%); mp 118-122°C (Recrystallised with benzene); IR $cm^{-1}$ (KBr) 3380, 3010, 1739, 1600, 1557, 1530, 1450, 1423, 1344, 803; $^1$H-NMR (DMSO-$d_6$), δ/ppm 7.7-7.9 (m, 4H, Ar-H), 8.1 (m, 4H, Ar-H), 8.3-8.5 (m, 2H, NH); Anal. Calcd for $C_{15}H_{10}N_4O_5$; C, 55.22; H, 3.09; N, 17.17. Found; C, 55.30; H, 3.30; N, 17.10.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-carboxyphenyl)urea (6e):**

Yield 2.20 g (96.8%); mp 215°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3342, 3012, 3000, 1721, 1675, 1600, 1570, 1550, 1427, 1289, 769; $^1$H-NMR (DMSO-$d_6$), δ/ppm 7.7-7.8 (m, 4H, Ar-H), 8.1 (m, 4H, Ar-H), 8.3-8.5 (m, 2H, NH), 11.0 (s, 1H, COOH); Anal. Calcd for $C_{16}H_{11}N_3O_5$; C, 59.08; H, 3.41; N, 12.92. Found; C, 59.32; H, 3.65; N, 12.66.

**1-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(4-methoxyphenyl)urea (6f):**

Yield 0.78 g (35.9%); mp >260°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr): 3329, 3017, 1770, 1715, 1600, 1580, 1500, 1450, 1250, 1058, 803; $^1$H-NMR (DMSO-$d_6$), δ/ppm: 3.7(s, 3H, $OCH_3$), 6.7 (d, *J*= 9.0 Hz, 2H, Ar-H), 7.5-7.7 (m, 4H, Ar-H), 8.1 (d, *J*= 8.9 Hz, 2H, Ar-H), 8.3-8.5 (m, 2H, NH); Anal. Calcd for $C_{16}H_{13}N_3O_4$; C, 61.73; H, 4.20; N, 13.50. Found; C, 60.92; H, 4.58; N, 13.74.

**3-(1,3-Dioxo-1,3-dihydroisoindol-2yl)-1-(4-chlorophenyl)-1-methylurea (6g):**

Yield 1.31 g (57%); mp 155°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3300, 3015, 1697, 1639, 1593, 1537, 1493, 1404, 831, 803, 682; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (s, 3H, N-$CH_3$), 7.2 (d, *J*= 9.0 Hz, 2H, Ar-H), 7.6-7.7 (m, 4H, Ar-H), 8.1 (d, *J*= 9.1 Hz, 2H, Ar-H), 8.4 (s, 1H, NH); Anal. Calcd for $C_{16}H_{12}N_3O_3Cl$; C, 58.28; H, 3.67; N, 12.74. Found; C, 58.00; H, 3.89; N, 12.87.

**3-(1,3-Dioxo-1,3-dihydroisoindol-2yl)-1-(4-bromophenyl)-1-methylurea (6h):**

Yield 0.86 g (33.2%); mp 240-241°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3290, 3016, 2954, 1770, 1710, 1590, 1570, 1440, 803, 570; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (s, 3H, N-$CH_3$), 7.4-7.7 (m, 6H, Ar-H), 8.1 (d, *J*= 9.3 Hz, 2H, Ar-H), 8.4 (s, 1H, NH) Anal. Calcd for $C_{16}H_{12}N_3O_3Br$; C, 51.36; H, 3.23; N, 11.23. Found; C, 51.42; H, 3.40; N, 11.00.

**3-(1,3-Dioxo-1,3-dihydro-isoindol-2yl)-1-(4-nitrophenyl)-1-methylurea (6i):**

Yield 1.67 g (70%); mp 105°C (Recrystallised with EtOH); IR $cm^{-1}$ (KBr) 3371, 3012, 2920, 1750, 1723, 1570, 1531, 1458, 1393, 1250 800; $^1$H-NMR (DMSO-$d_6$), δ/ppm 2.8 (s, 3H, N-$CH_3$), 7.7-7.9 (m, 4H, Ar-H), 8.1 (m, 4H, Ar-H), 8.4 (s, 1H, NH); Anal. Calcd for $C_{16}H_{12}N_4O_5$; C, 56.47; H, 3.55; N, 16.46. Found;

C, 56.40; H, 3.78; N, 16.66.

**Anti-viral Screening**

The final products (**6a-i**) were tested *in vitro* against a variety of viruses (Herpes simplex virus-1(KOS), Herpes simplex virus-2 (G), Vaccinia virus, Vesicular stomatitis virus, Herpes simplex virus-1 $TK^{-1}$ KOS $ACV^{r}$, Coxsackie virus B4, Respiratory syncytical virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus) and the results were compared with standard drugs (*cf*. Table 1, 2 and 3). Cytotoxicity and anti-viral activity of the compounds have been performed in HEL, HeLa and Vero cell culture adopting a standard methodology.[60]

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