JEIMC 23,476-482 (2008)

Synthesis of azatricyclodiones & octahydro-benzo[f]isoindoles and their antimicrobial evaluation

Nisha Saxena[1], Nimisha Singh[1], Mridul Mishra[1], G.B. Shiva Keshava[2], Praveen Kumar Shukla[2] and Rama Pati Tripathi[1]*

[1]*Medicinal and Process Chemistry Division and* [2]*Fermentation Technology Division*

Central Drug Research Institute, Lucknow-226001, India

*Correspondence: Dr. Rama Pati Triapthi

Medicinal and Process Chemistry Division Central Drug Research Institute, Lucknow-226001, India

Email: rpt_56@yahoo.com; rpt.cdri@gmail.com; Telphone No.: +91 522 2612412; Fax: +91 522 2623405/262938;

Abstract.

A series of azatricyclodiones and octahydro-benzo[f]isoindoles have been synthesized by (4+2) *Diels-Alder* cycloaddition of maleimides with furfuryl amine. Reaction of azatricyclodiones with isocyanates led to respective ureides. All of the compounds were screened against a number of bacteria and fungi. One of the compounds (**2)** displayed moderate Antitubercular activity while two compounds (**2)** and (**4)** inhibited the fungal growth at 25 μg/mL.

Keywords: *Cycloaddition, dienophile, furfuryl amine, azatricyclodiones, octahydro-benzo[f]isoindoles*

Introduction.

The Diels-Alder reaction is widely used to construct six-membered carbon skeletons in a wide variety of organic compounds of biological importance [1,2]. Maleimides have been used as dienophile in many cycloaddition reactions to get molecules of chemotherapeutic importance. Moreover, maleimides, themselves are well known as antifungal agents and many of them have potential as drugs [3]. Protein kinases are implicated in a number of biological processes and are the hot targets to explore new drugs and it is established that maliemides inhibit protein kinases [3c]. Furan ring on the other hand is very common in natural products and pharmaceuticals. The synthetic application of Diels–Alder chemistry to furan derivatives has been extensively studied and successfully exploited in conventional organic solvents [4]. Synthesis of substituted 7-oxa-norborn-2-enes by reaction of maleic anhydride and furfuryl alcohol has opened a new chapter for interesting biologically active molecules [5]. The above reports and our quest for new antituberculars [6,7] prompted us to synthesize the hybrid structures, consisting of fused maleimide and furan rings, the azatricyclodiones & octahydro-benzo[f]isoindoles and screen them against a number of pathogens. The compounds have been synthesized using N-phenyl maleimides as dienophile and furfuryl amine as diene followed by further modifications of the amines.

Materials

All the chemicals were supplied by Merck (Germany) and S.D fine chemicals (India). Purity of compounds was checked on thin layer chromatography (silica gel G) in solvent system hexane-ethyl acetate (6:4) and methanol-chloroform (2:8) and the spots were located under iodine vapours or UV light. Melting points were determined on a Buchi 510 apparatus. Elemental analysis for all the compounds were performed on a Carlo Erba Model EA-1108 elemental analyzer and data of C, H, and N is within ±0.4% of calculated values. IR(KBr) spectra were recorded using Perkin-Elmer 881 spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded on a Jeol (Japan) SX 102/DA-6000 Mass Spectrometer/Data system. The ^{1}H NMR spectra were recorded on Brucker Spectrospin spectrometer at 200 using TMS as

internal standard. The chemical shift values are on δ scale and the coupling constants (*J*) are in Hz.

Methods.

Chemistry

*General method for the preparation of 1-aminomethyl-4-(substituted)phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (***2**,**4**,**6**,**8**,**10***)* and *4,8-diaminomethyl-4,9-5,8-diepoxy-2-(susbstituted)phenyl-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole* (**3**, **5**, **7**, **9**, **11**, and **12**): To the solution of appropriate starting maleimide (**1a-1g)** (5.78mmol) in toluene (7 mL), at 80º C and 1 equivalents of furfuryl amine (0.50 mL, 5.78 mmol) for 2-3 hr till the complete disappearance of starting material (TLC). The solvent was evaporated under reduced pressure and the residue, so obtained, was dissolved in chloroform (15mL) washed with water (2 x 10 mL), saturated NaCl solution (2 x 20mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get a crude product which was chromatographed over SiO_2 using hexane: ethyl acetate to afford the respective compounds **2**,**4**,**6**,**8**, and **10.** Further, elution of the column with chloroform: methanol (8:2) gave the compounds **3**, **5**, **7**, **9**, **11**, and **12**.

Compounds **3**, **5**, **7**, **9**, were obtained exclusively when two equivalents of furfuryl amines were reacted separately with **1a-1d**. Compounds **11**, and **12** were similarly prepared from malimides **1f** and **1g**.

1-Aminomethyl-4(-phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (**2**): white granules (76%) yield, mp 90-95° C. IR: (KBr) cm^{-1} 3459, 3287; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 5H, ArH), 6.34 (two d, J=2.9 Hz and J=1.7 Hz, 1H, H-8), 6.26 (d, J=2.9 Hz,, 1H, H-9), 3.90 (m, 3H, NCH_2 and H-7), 3.07 (d, J=8.3Hz, 1H, H-6), 2.97 (d, J=8.3 Hz, 1H, H-2), 2.69 (d, J=5.3 Hz, 1H, H-6), 2.62 (d, J=5.3 Hz, 1H, H-2) 2.1(bs, 1H, NH); MS m/z = 271 $(M+H)^+$; Cal/Ana. [$C_{15}H_{14}N_2O_3$: C (66.66) 66.09, H (5.18) 5.11,N (10.37) 10.30].

1-Aminomethyl-4-(4-methyl phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (**4**): yellow powder (74%); mp 100-102° C. IR: (KBr) cm^{-1} 3293, 1602, 753; ^{1}H-NMR

(200 MHz, $CDCl_3$): δ 7.28 (d, J=8.1 Hz, 2H, ArH), 7.15 (d, J=8.2 Hz, 2H, ArH), 6.34 (two d, $J_{8,9}$ =2.9 Hz and $J_{8,7}$ =1.7 Hz, 1H, H-8), 6.25 (d, $J_{8,9}$ =2.9 Hz,, 1H, H-9), 3.94-3.85 (m, 3H, NCH_2 and H-7), 3.08 (d, $J_{2,6}$ =8.3Hz, 1H, H-6), 2.99 (d, $J_{6,2}$ =8.3 Hz, 1H, H-2), and for IInd exoisomer 2.69 (d, $J_{2,6}$ =5.3 Hz, 1H, H-6), 2.60 (d, $J_{6,2}$ =5.2 Hz, 1H, H-2) 2.1(bs, 1H, NH); MS m/z = 285 $(M+H)^+$; Cal/Ana [$C_{16}H_{16}N_2O_3$: C (67.60) 67.50,H (5.63) 5.56,N (9.85) 9.80].

1-Aminomethyl-4-(2-methyl phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione ***(6).*** white crystals (76%); mp 78-80° C. IR (KBr): ν_{max} ; *IR: (KBr) cm^{-1}* 3459, 3287; *^{1}H-NMR (200 MHz, $CDCl_3$)*: δ 7.40 (*m*, 4H, *ArH*), 6.35 (*two d*, $J_{8,9}$=2.8 Hz and $J_{8,7}$=1.6 Hz, 1H, *H-8*), 6.26 (*d*, $J_{8,9}$=3.0 Hz, 1H, *H-9*), 4.02 (*m,* 3H, N*CH$_2$* and *H-7*), 3.03 (*d*, $J_{2,6}$ =5.9 Hz, 1H, *H-6*), 2.99 (*d*, $J_{6,2}$=5.8 Hz, 1H, *H-2*), 2.73 (*d*, $J_{2,6}$=5.1 Hz, 1H, *H-6*), 2.64-2.62 (*d*, $J_{6,2}$ =5.1 Hz, 1H, *H-2*), 2.4 (*bs*, 1H, *NH*), 2.1 (*s*, 3H, *CH_3*), and 2.1 (*s*, 3H, *CH_3*); MS *m/z* = 285 *$(M+H)^+$*; Cal/Ana [$C_{16}H_{16}N_2O_3$: C (67.60) 67.59, H (5.63) 5.58, N (9.85) 9.80].

1-Aminomethyl-4-(2,6-dichlorophenyl)10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione ***(8).*** white powder (73.9%) yield; mp 100-102° C. *IR: (KBr) cm^{-1}* 3459, 3287; *^{1}H-NMR (200 MHz, $CDCl_3$)* : δ 7.47 (*m*, 3H, *ArH*), 6.36 (*two d*, $J_{8,9}$=3.0 Hz and $J_{8,7}$=1.7 Hz, 1H, *H-8*), 6.28 (*d*, $J_{8,9}$=2.9 Hz, 1H, *H-9*), 4.13 (*m,* 3H, N*CH$_2$* and *H-7*), 3.18 (*d*, $J_{2,6}$=8.3 Hz, 1H, H-6), 3.11 (*d*, $J_{6,2}$ =8.3 Hz, 1H, *H-2*), 2.82 (*d*, $J_{2,6}$=5.6 Hz, 1H, *H-6*), 2.73 (*d*, $J_{6,2}$=5.6 Hz, 1H, *H-2*), 2.3 (*bs*, 1H, *NH*); MS *m/z* = 339 *$(M+H)^+$* ; Cal/Ana [$C_{15}H_{12}N_2O_3Cl_2$: C, (53.25) 53.20,H (3.55) 3.45,N (8.28) 8.35].

1-Aminomethyl-4-(4-methoxy-phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione ***(10).*** white powder (72%) yield; mp 123-125 °C. *IR: (KBr) cm^{-1}* 3306, 1708, 1513; *^{1}H-NMR (200 MHz, $CDCl_3$)* : δ 7.40 (*m*, 4H, *ArH*), 6.35 (*two d*, $J_{8,9}$ =1.9 Hz and $J_{8,7}$ =1.8 Hz, 1H, *H-8*), 6.27 (*d*, $J_{8,7}$ =2.9 Hz, 1H, *H-9*), 3.99 (*m,* 3H, N*CH$_2$* and *H-7*), 3.10 (*d*, $J_{2,6}$ =8.3 Hz, 1H, *H-6*), 3.01 (*d*, $J_{6,2}$=8.3 Hz, 1H, *H-2*), 2.70 (*d*, $J_{2,6}$=5.2 Hz, 1H, *H-6*), 2.61 (*d*, $J_{6,2}$ =5.9 Hz, 1H, *H-2*), 1.75 (*bs*, 1H, *NH*); ; MS *m/z* = 302*$(M+H)^+$* ; Cal/Ana [$C_{16}H_{16}N_2O_4$: C (64.12) 64.11,H (5.34) 5.30,N (9.30) 9.25].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-phenyl-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(3).*** Light brown crystals (90%) yield mp 87-90°C. *IR: (KBr) cm*$^{-1}$ 3293, 1700, 1598, 1351; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.55 (*m*, 5H, *ArH*), 7.10 (*m*, 2H, *H-6* and *H-7*), 6.27 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.42 (*m*, 2H, N*CH$_2$*), 3.85 (*m,* 2H, N*CH$_2$*), 3.56 (*m*,1H, *H-9*), 2.71 (*m*, 2H, H-3^a and *H-9a*), 2.0 (*bs*, 1H, *NH*); MS *m*/*z* = 368*(M+H)*$^+$; Cal/Ana [$C_{20}H_{21}N_3O_4$: C (65.39) 65.45,H (5.72) 5.78,N (11.44) 11.36].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-(4-methyl phenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(5).*** white powder (91%) yield; mp 118-122° C. *IR: (KBr) cm*$^{-1}$ 3293, 1700, 1598, 1351; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.69 (*m*, 4H, *ArH*), 7.10 (*m*, 2H, *H-6* and *H-7*), 6.28 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.41 (*m*, 2H, N*CH$_2$*), 3.848 (*m,* 2H, N*CH$_2$*), 3.54 (*m*,1H, *H-9*), 2.69 (*m*, 2H, *H-3a* and *H-9a*), 2.1 (*s*, 3H, *CH$_3$*),and 2.30 (*s*, 3H, *CH$_3$*), 2.0 (*bs*, 1H, *NH*); MS *m*/*z* = 382*(M+H)*$^+$; Cal/Ana [$C_{21}H_{23}N_3O_4$: C, (66.14) 66.08,H (6.03) 6.13,N (11.02) 11.12].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-(2-methyl phenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(7)*** white powder (90%); mp 118-122° C. *IR: (KBr) cm*$^{-1}$ 3404,2819, 1596, 1352; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.95-7.19 (*m*, 4H, ArH), 7.16 (*m*, 2H, *H-6* and *H-7*), 6.30 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.41 (*m*, 2H, N*CH$_2$*), 3.87 (*m,* 2H, N*CH$_2$*), 3.56 (*m*,1H, *H-9*), 2.74 (*m*, 2H, *H-3a* and *H-9a*), 2.26 (*s*, 3H, *CH$_3$*),and 2.20 (*s*, 3H, *CH$_3$*), 2.0 (*bs*, 1H, *NH*); MS *m*/*z* = 382*(M+H)*$^+$; Cal/Ana [$C_{21}H_{23}N_3O_4$: C (66.14) 66.08,H (6.03) 6.13,N (11.02) 11.12].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-(2,6-dichloro-phenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(9).*** white granules (86%) yield; mp 119-123° C. *IR: (KBr) cm*$^{-1}$ 3293, 1638, 1522, 1350; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.32-7.24 (*m*, 3H, *ArH*), 7.15 (*m*, 2H, *H-6* and *H-7*), 6.29 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.37 (*m*, 2H, N*CH$_2$*), 3.91 (*m,* 2H, N*CH$_2$*), 3.71 (*m*,1H, *H-9*), 2.72 (*m*, 2H, *H-3a* and *H-9a*), 2.0 (*bs*, 1H, *NH*); MS *m*/*z* = 436*(M+H)*$^+$; Cal/Anar [$C_{20}H_{19}N_3O_4Cl_2$: C (55.17) 55.12,H (4.36) 4.30,N (9.65) 9.70].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-(3-bromo-phenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(11).*** viscous liquid (85%) yield; *IR: (KBr)* cm^{-1} 3293, 1700, 1598, 1351; ^{1}*H-NMR (200 MHz, CDCl$_3$)* : δ 7.82 (*m*, 1H, *ArH*), δ 7.436 (*m*, 3H, *ArH*), 7.21 (*m*, 2H, *H-6* and *H-7*), 6.27 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.43 (*m*, 2H, N*CH$_2$*), 3.85 (*m,* 2H, N*CH$_2$*), 3.52 (*m*,1H, *H-9*), 2.69 (*m*, 2H, *H-3a* and *H-9a*), 2.3 (*bs*, 1H, *NH*); MS *m*/*z* = 448*(M+H)*$^+$; Cal/Ana [$C_{20}H_{20}N_3O_4Br$: C (53.57) 53.50,H (4.46) 4.49,N (9.37) 9.39].

4,8-Diaminomethyl-4,9-5,8-diepoxy-2-(3-methoxy-phenyl)-3a,4,4a,5,8,8a,9,9a-octahydro-benzo[f]isoindole ***(12).*** white crystals (80%) yield; mp 100-101° C. *IR: (KBr)* cm^{-1} 3293, 1700, 1598, 1351; ^{1}*H-NMR (200 MHz, CDCl$_3$)* : δ 7.29 (*m*, 4H, *ArH*), 7.06 (*m*, 2H, *H-6* and *H-7*), 6.23 (*m*, 3H, *H-4a*, *H-5*, *H-8a*), 4.37 (*m*, 2H, N*CH$_2$*), 3.79 (*m,* 2H, N*CH$_2$*), 3.73 (*s*, 3H, O*CH$_3$*), 3.46 (*m*,1H, *H-9*), 2.65 (*m*, 2H, *H-3a* and *H-9a*), 2.0 (*bs*, 1H, *NH*); MS *m*/*z* = 399*(M+H)*$^+$; Cal/Ana [$C_{21}H_{22}N_4O_7$: C (57.01) 57.15,H (4.97) 4.90,N (12.66) 12.70].

General method of preparation of compounds ***(13-22)*** *1-(4-Chloro-phenyl)-3-(3,5-dioxo-4-(substituted)phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea.*

A solution of the above compounds (**2,4, 8** and **10**) in (1.11mmol) and selected phenylisocyanates (1.14 mmol) in dry CH_2Cl_2 (2mL) was magnetically stirred at ambient temperature for 5-10 hr till the complete disappearance of starting material (TLC). The solvent was evaporated under reduced pressure and the residue so obtained was dissolved in chloroform (10mL) washed with water (2 x 5 mL), saturated NaCl solution (2 x 5 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to get a crude product was chromatographed over SiO_2 using hexane: ethyl acetate (7:3) to give desired compounds.

1-(4-Chloro-phenyl)-3-(3,5-dioxo-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(13).*** white crystals (85.28%) yield, mp 170-173°C. *IR: (KBr)* cm^{-1} 3356, 1722, 1677, 1599; ^{1}*H-NMR (200 MHz, CDCl$_3$)* : δ 7.54 (*m*, 9H, *ArH*), 6.36 (*d*, *J*=2.9 Hz 1H, *H-9*), 6.31 (*d*, *J*=1.76 Hz 1H, *H-8*), 4.95(*d, J* = 15.8 Hz, 1H, N*CH$_2$*), 4.46 (*d*, *J* = 15.8Hz, 1H, N*CH$_2$*), 4.34 (*t*, *J* = 4.3 Hz and *J* =4.3 Hz, 1H, *H-7*), 3.19 (*m*, 2H, *H-2* and *H-*

6), 2.0 (*bs*, 2H, *NH*); MS *m/z* = 424*(M+H)*$^+$; Cal/Ana [$C_{22}H_{18}N_3O_4Cl$: C (62.41) 62.35,H (4.25) 4.29,N (9.92) 9.99].

1-(4-Chloro-phenyl)-3-(3,5-dioxo-4-(4-methyl phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(14).*** white crystals (85%) yield, mp 175-180°C. *IR: (KBr) cm^{-1}* 3402,3309, 2362, 1600, 1349; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.48 (*m*, 8H, *ArH*), 6.36 (*d*, *J*=2.9 Hz 1H, *H-9*), 6.33 (*t*, *J*=1.76 Hz and *J*=3.16 Hz, 1H, *H-8*), 4.95 (*d, J*= 15.8 Hz, 1H, N*CH$_2$*), 4.46 (*d*, *J* = 15.8 Hz, 1H, N*CH$_2$*), 4.35 (*t*, *J* = 4.3Hz and *J* =4.3 Hz, 1H, *H-7*), 3.12 (m, 2H, *H-2* and *H-6*), 2.17 (*s*, 3H, *CH$_3$*), 1.8 (*bs*, 2H, *NH*); MS *m/z* = 422*(M+H)*$^+$; Cal/Ana [$C_{23}H_{20}N_3O_4Cl$: C (63.15) 63.10,H (4.57) 4.61,N (9.61) 9.88].

1-(4-Methoxy-2-nitro-phenyl)-3-(3,5-dioxo-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(15).*** white crystals (87%) yield, mp 95-96°C. *IR: (KBr) cm^{-1}* 3402, 1600, 1349, 747; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.58 (*m*, 8H, *ArH*), 6.31 (*m*, 2H, *H-8* and *H-9*), 4.83 (*m,* 1H, N*CH$_2$*), 4.50 (*m,* 2H, N*CH$_2$* and *H-7*), 3.83 (*s,* 3H, -O*CH$_3$*), 2.97 (*m* ,2H, *H-2* and *H-6*) 2.14 (*bs*, 2H ,*NH*); MS *m/z* = 465*(M+H)*$^+$; Cal/Ana [$C_{23}H_{20}N_4O_7$: C (59.48) 59.40,H (4.31) 4.25,N (12.06) 12.12].

1-(4-Methoxy-2-nitro-phenyl)-3-(3,5-dioxo-4-(4-methyl phenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(16)*** . Yellow crystals (81%) yield, mp 85-87°C. *IR: (KBr) cm^{-1}* 3429, 1596, 1351, 760; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.59 (*m*, 7H, *ArH*), 6.32 (*s*,1H), 6.27 (*m,* 2H, *H-8* and *H-9*), 4.77 (*m,* 1H, N*CH$_2$*), 4.51 (*m,* 2H, N*CH$_2$* and *H-7*), 3.84 (*s,* 3H, -O*CH$_3$*), 2.97 (*m* ,2H, *H-2* and *H-6*) 2.14 (*bs*, 2H, *NH*), 2.28 (*s,* 3H, *CH$_3$*), 2.04 (*bs*, 2H, *NH*); MS *m/z* = 479*(M+H)*$^+$; cal/Ana [$C_{24}H_{22}N_4O_7$: C (60.25) 60.20,H (4.60) 4.72,N (11.71) 11.65].

1-(4-Methoxy-2-nitro-phenyl)-3-(3,5-dioxo-4-(2,6-dichlorophenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(17).*** yellow crystals (83%) yield, mp 199-200°C. *IR: (KBr) cm^{-1}* 3390, 1724, 1596, 786; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.61 (*m*, 6H, *ArH*), 6.42 (*m,* 2H, *H-8* and *H-9*), 5.10 (*d, J*=15.6 Hz, 1H, N*CH*), 4.47 (*d, J*=15.8 Hz, 1H, N*CH*), 4.27 (*m,* 1H, *H-7*), 3.89 (*s,* 3H, O*CH$_3$*) 3.15 (*m*, 2H, *H-2* and *H-6*), 2.02 (*bs*, 2H,

NH); MS *m/z* = 533*(M+H)*$^+$; Cal/Ana [$C_{23}H_{18}N_4O_7Cl_2$: C (51.87) 51.76,H (3.38) 3.29,N (10.52) 10.46].

1-(3-Acetyl-phenyl)-3-(3,5-dioxo-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(18).*** white powder (84%) yield, mp 88-89°C. *IR: (KBr) cm*$^{-1}$ 3441, 1597, 1352, 763; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 8.09 (*m*, 9H, *ArH*), 6.31 (*d, J*=2.88 Hz, 1H, *H-9*), 6.27 (*t, J*=1.7 Hz and *J*=3.03 Hz, 1H, *H-8*), 4.84 (*d, J*=15.90 Hz, 1H, N*CH$_2$*), 4.51 (*d, J*=15.9 Hz, 1H, N*CH$_2$*), 4.38 (*t, J*=4.26 Hz and *J*=4.17 Hz, 1H, *H-7*), 3.01 (*m, J*=4.2 Hz, 2H, *H-2* and *H-6*), 2.55 (*s,* 3H CO*CH$_3$*), 2.04 (*bs*, 2H, *NH*); MS *m/z* = 432*(M+H)*$^+$; Cal/Ana [$C_{24}H_{21}N_3O_5$: C (66.82) 66.88,H (4.87) 4.96,N (9.74) 9.70].

1-(3-Acetyl-phenyl)-3-(3,5-dioxo-4-(4-methyl phenyly)l-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(19).*** whitish yellow crystals (86%) yield, mp 167-169°C. *IR: (KBr) cm*$^{-1}$ 3430, 1715, 1597, 759; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 8.03 (*m*, 8H, *ArH*), 6.32 (*d, J*=2.7 Hz, 1H, *H-9*), 6.28 (*t, J*=1.6 Hz and *J*=3.0 Hz, 1H, *H-8*), 4.85 (*dd,* J=15.9 Hz and J=15.9 Hz, 2H, N*CH$_2$*), 4.39 (*t, J*=4.2 Hz and *J*=4.2 Hz, 1H, *H-7*) 2.99 (*d, J*=4.3 Hz, 2H, *H-2* and *H-6*) 2.56 (*s,* 3H, CO*CH$_3$*), 2.27 (*s,* 3H, *CH$_3$*), 1.9 (*bs*, 2H, *NH*); MS *m/z* = 446*(M+H)*$^+$; Cal/Ana [$C_{23}H_{23}N_3O_5$: C (67.41) 67.35,H (5.16) 5.22,N (9.43) 9.32].

1-(2-Fluoro-phenyl)-3-(3,5-dioxo-4-phenyl-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(20).*** White powder (89%) yield, mp 205-207°C. *IR: (KBr) cm*$^{-1}$ 3420, 1718, 1597 ; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.64 (*m*, 9H, *ArH*), 6.29 (*m*, 2H, *H-9* and *H-8*), 4.83 (*d, J* = 15.8 Hz, 1H, N*CH$_2$*), 4.49 (*d*, *J* = 15.8 Hz, 1H, N*CH$_2$*), 4.13 (*t*, *J* = 4.3 Hz and *J* =4.3 Hz, 1H, *H-7*), 3.00 (*m*, 2H, *H-2* and *H-6*), 2.0 (*bs*, 2H, *NH*); MS *m/z* = 391*(M+H)*$^+$; Cal/Ana [$C_{22}H_{18}N_3O_4F$: C (67.69) 67.82,H (4.61) 4.61,N (10.76) 10.70].

1-(4-Chloro-phenyl)-3-(3,5-dioxo-4-(4-methoxyphenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea ***(21)*** white crystals (92.8%) yield, mp 170-173°C. *IR: (KBr) cm*$^{-1}$ 3420, 1718, 1597; *^{1}H-NMR (200 MHz, CDCl$_3$)* : δ 7.53 (*m*, 8H, *ArH*), 6.83 (*d, J*=8.9 Hz, 1H, *H-9*), 6.33 (*d, J*=2.6 Hz, 1H, *H-8*), 4.86 (*d, J*=15.9 1H, N*CH$_2$*), 4.53 (d, *J*=15.89 Hz, 1H, N*CH$_2$*), 4.37 (*t, J*=4.36 and *J*= 4.39 Hz, 1H, *H-7*), 3.77

(*s*, 3H, CH_3), 2.97 (*m*, 2H, *H-2* and *H-6*), 1.81 (*bs*, 1H, *NH*); MS *m/z* = 455$(M+H)^+$; Cal/Ana [$C_{23}H_{20}N_3O_5Cl$: C (64.12) 60.79,H (5.34) 5.4,N (9.30) 9.25].

1-(4-Fluoro-phenyl)-3-(3,5-dioxo-4-(4-methoxyphenyl)-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-1-ylmethyl)-urea ***(22).*** white powder (75.7%) yield, mp 170-173°C. *IR: (KBr)* cm^{-1} 3420, 1718, 1597; ^{1}*H-NMR (200 MHz, CDCl$_3$)* :, 7.46 (*m*, 8H, *ArH*), 6.86 (*d, J*=8.9 Hz, 1H, *H-9*), 6.35 (*d, J*=3.8 Hz, 1H, *H-8*), 4.88 (*d, J*=15.9 1H, NCH_2), 4.59 (d, *J*=15.9 Hz, 1H, NCH_2), 4.47 (*t, J*=4.51 and *J*=4.48 Hz, 1H, *H-7*), 3.78 (*s*, 3H,), 3.00 (*d, J*=4.28 Hz, 2H, *H-2 and H-6*), 1.65 (*bs*, 1H, *NH*); MS *m/z* = 438$(M+H)^+$; Cal/Ana [$C_{23}H_{20}N_3O_5F$: C (64.12) 63.01,H (5.34) 5.57,N (9.30) 9.61].

Results and Discussion.

Chemistry

The starting dienophile *N*-phenyl maleimides (**1a-1g**) were prepared following earlier protocol [8, 9] as shown in Scheme 1.

Please insert Scheme 1

Thus reaction of N-phenyl maleimides (**1a-1e**) with one equivalent of furfuryl amine in benzene at 80°C in toluene led to the formation of respective azatricyclodiones **2** [10], **4**, **6**, **8** and **10** as major products in varying yields along with minor amount of octahydro-benzo[f]isoindoles **3**, **5**, **7** and **9** with maleimides **1a-1d**. The respective octahydro-benzo[f]isoindole could not be detected during reaction of furfuryl amine with maleimide **1e**. Although there are few reports for the above azatricyclodiones in such reactions, yet the octahydro-benzo[f]isoindoles are novel structures and being reported in this reaction for the first time. The octahydro-benzo[f]isoindoles **3**, **5**, **7, 9**, could also be obtained as the only product of the reaction of one equivalent of dienophile **1a-d** with two equivalents of furfuryl amine separately. Similarly reaction of 1f and 1g with two equivalents of furfuryl amine led to the formation of respective octahydro-benzo[f]isoindoles **11**,**12** in good yields.

Although the possibilities of four stereomers two *endo*- and two *exo* exist in this reaction, yet the major product isolated was found to be almost 1:1 mixture of two *exo*-isomers (**Figure 1)**.The structures of the isolated products were based on the ^{1}H NMR spectra of the compounds and the earlier report on such compounds [18]. In the ^{1}H NMR spectrum of compound **2,** H-6 was observed as two d at δ3.07 ($J_{2,6}$=8.3 Hz) and 2.69 ($J_{2,6}$=5.6 Hz) in the two exoisomers, while H-2 for the two exoisomers appeared at δ2.97 ($J_{6,2}$=8.3 Hz) and 2.62 ($J_{6,2}$=5.6 Hz) similar to the above report [18]. Since we did not observe any coupling between H-6 and H-7 in the ^{1}H NMR spectrum of the compound it further substantiates the structure of compound **2** as a mixture of two exo-isomers. H-7 was mixed with the multiplet of CH_2NH_2 protons, while the olefinic H-8 was observed at as two d at δ6.34 ($J_{8,9}$ =2.9 Hz) and δ 6.33 ($J_{8,7}$ =1.7 Hz), and H-9 appeared as a d δ 6.26 ($J_{8,9}$=2.9 Hz) at and δ 2.62 ($J_{6,2}$=5.6 Hz). A *m at* δ 7.35 accounted for 5 aromatic protons and the exchangeable NH was observed as a *bs* at δ 2.1. Similar pattern was observed in all the compounds.

The ^{1}H-NMR spectrum of octahydro-benzo[f]isoindole (**3**) displayed aromatic protons as a multiplet (δ 7.55-7.25), (*m*, 5H, ArH), 7.10-7.08 (*m*, 2H, H-6 and H-7), 6.27-6.16 (*m*, 3H, H-4a, H-5, H-8a), 4.42-4.36 (*m*, 2H, NCH_2), 3.85-3.79 (*m,* 2H, NCH_2), 3.56-3.48 (*m*,1H, H-9), 2.71-2.63 (*m*, 2H, H-3^a and H-9a), 2.0 (*bs*, 1H, NH). The isolated products have been presumed to be exo-isomers based on literature precedent where formation of thermodynamically controlled exo-isomers predominates during reaction of maleimides with furfuryl alcohol [14].

Please insert Scheme 2

Please insert Figure 1

Ureides (**13-22**) **(Scheme 3)** were prepared in very good yields by reaction of the equimolar amounts aza-tricyclic diones **2**, **4**, **8** and **10** with 4-chlorophenyl-, 2-flurophenyl-, 4-fluorophenyl-, 3-acetylphenyl-, 2-nitro-4-methoxyphenyl-isocyantes separately in CH_2Cl_2 under anhydrous condition.

Please insert Scheme 3

All the compounds synthesized were evaluated against *Mycobacterium tuberculosis H37Ra* [12] and *Mycobacterium tuberculosis Rv* strains [13], *Klebsiella pneumoniae*, *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* strains of bacteria and *Candida albicans Cryptococcus neoformans Sporothrix schenckii Trichophyton mentagrophytes Aspergillus fumigatus Candida parapsilosis* (ATCC-22019) strains of fungi [14]. Antibacterial and antifungal screening results are shown in Table 1.

The antimycobacterial acticity of the above compounds was not very encouraging as the only compound **2** possess moderate antimycobacterial activity (MIC of 12.5 µg/mL) against the virulent strain of *Mycobacterium tuberculosis H37Rv*. Further, only one compound **9** which exhibited a mild antibacterial activity against *E.coli* where as few of them had mild antifungal activity. Of these, compound no. **2** and **4** exhibited *in vitro* antifungal activity against *T. mentagrophytes* at 25µg/ mL. (*Table 1*)

Acknowledgements

Authors are thankful to Tuberculosis research group for Antitubercular activity. N.S. and N.S are thankful to the CSIR, New Delhi, for SRF and Project Assistantship from the DRDO Project No. ERIP/ER/0502127/M/011857), New Delhi.

References.

[1].Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford **1990**.

[2]. (a) Mulzer, J.; Altenbach, H.J.; Braum, M.; Krohn, K.; Reissig, H.U. *Organic Synthesis Highlights*., Verlag Chemie, Weinheim., **1991,** pp. 54-70. (b) (**d**). Vogel, P.; Cossy, J.; Plumet J. and Arjona, O. Derivatives of 7-oxabicyclo[2.2.1]heptane in nature and as useful synthetic intermediates *Tetrahedron.* **1999**, *55*, 13521.

[3].(**a**). Zhang, H. C.; Derian, C. K.; McComsey, D. F.; White, K. B.; Ye, H.; Hecker, L. R.; Li, J.; Addo, M. F.; Croll, D.; Eckardt, A. J.; Smith, C. E.; Li, Q.; Cheung, W-M.; Conway, B.R.; Emanuel, S.; Demarest, K. T.; Gordon, P.A.; Damiano, B. P. and Maryanoff, B. E. Novel Indolylindazolylmaleimides as Inhibitors of Protein Kinase C-$^{\beta}$: Synthesis, Biological Activity, and Cardiovascular Safety *J. Med. Chem.,* **2005,** *48,* 1725-1728. (**b**). Kalgutkar, A. S.; Crews, B.C. and Marnett, L. J. Design, Synthesis, and Biochemical Evaluation of *N*-Substituted Maleimides as Inhibitors of Prostaglandin Endoperoxide Synthases *J. Med. Chem*., **1996**, *39*, 1692-1703. (**c**). Gayoso, C. W.; Lima, E. De O.; de Souza, E. L., Filho, V.C.; Trajano, V. N.; Pereira, F. de Oliveira; Lima, I. O. Antimicrobial Effectiveness of Maleimides on Fungal Strains Isolated from Onychomycosis *Braz. Arch. Biol.Tech.,* **2006,** *.49*, 661-664.

[4]. Kappe, C. O.; Murphree, S. S. and Padwa, A. Synthetic applications of furan Diels-Alder chemistry *Tetrahedron.*, **1997**, *53*,14179 (b) Tarducci, C.; Badyal, J. P. S.; Brewer, S. A.; Willis, C. Diels–Alder chemistry at furan ring functionalized solid surfaces*Chem. Commun*. **2005**, 406–408

[5]. (**a**). Nottori, N.;. Kato, T.; Asano, Y.;Ueda, M.; Kirino, O.; Ooba, S.; Fujinami, A. and Ozaki, T. *Fungicidal Norbornanes and oxabicycloheptanes.*, **1974**, *890*, 72109. (**b**). Vogel, P.; Cossy, J.; Plumet J. and Arjona, O. Derivatives of 7-oxabicyclo[2.2.1]heptane in nature and as useful synthetic intermediates *Tetrahedron.* **1999**, *55*, 13521.(**c**) Bailey,

T. R.; Rippin, S. R.; Opsitnick, E.; Burns, C. J.; Pevear, D. C.; Collett, M. S.; Rhodes, G.; Tohan, S.; Huggins, J. W.; Baker, R. O.; Kern, E. R.; Keith, K. A.; Dai, D.; Yang, G.; Hruby, D. and Jordan, R. N-(3,3a,4,4a,5,5a,6,6a-Octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2-(1H)-yl)carboxamides: Identification of novel orthopoxvirus egress inhibitors *J. Med. Chem. Letters.*, **2007**, 50, 1442-44

[6] (**a**)Tripathi, R. P.; Tewari, N.; Dwivedi, N.; Tiwari, V. K. Fighting Tuberculosis-An old disease with new Challenges *Med. Res. Rev*. **2005,** *25***,** 93-131.(**b**) Tripathi, R.P.; Katiyar, D.; Tiwari, V. K.; Tewari, N.; Verma, S. S.; Sinha, S.; Gaikwad, A.; Srivastava, A.; Chaturvedi, V.; Srivastava, B. S.; Tripathi, R. P. Synthesis and antitubercular activities of bis-glycosylated diamino alcohols *Eur. J. Med. Chem*., **2005**, *40*, 351-360. (**c**) Tripathi, R. P.; Tripathi, R.; Tiwari, V. K.; Bala, L.; Sinha, S.; Srivastava, A.; Srivastava, R.; Srivastava, B. S. Synthesis of glycosylated beta-amino acids as new class of antitubercular agents *Eur. J. Med. Chem*., **2002**, *37*, 773-781.

[7]. Tewari, N.; Tiwari,V. K. ; Mishra, R. C.; Tripathi, R. P.; Srivastava, A. K.; Ahmad, R.; Srivastava, R.; Srivastava, B. S. Synthesis and bioevaluation of glycosyl ureas as α-glucosidase inhibitors and their effect on Mycobacterium *Bioorganic Med. Chem* **2003**,*11*, , 2911-2922

[8] Koechel, D. A.; Tarloff, J. B.; Rankin, G. O. Acute effects of alkylating agents on canine and renal function: specifically designed synthetic maleimides *J. Med. Chem.* **1983**, *26*, 85-90.

[9] Tsou, K.-C.; Barrnett, R. J.; Seligman, A. M. Preparation of some N-(1-naphthyl maleimides) as sulfhydryl group reagents *J. Am. Chem. Soc.* **1955**, *77*, 4613-4616.

[10] Kondoli, J.C.; Prajapati, D.; Sandhu. J.S.; Wakefield, B.J. Varying pathways in the reactions of fufuryl amines with maleic anhydride and N-phenyl maleimide. *J. Chem. Res.(S)* **1987**, 76

[11] Jarosz, S.; Mach, M.; Szewczyk, K.; Zbigniew, S. S. Synthesis of Sugar-Derived 2′-and 3′-Substituted Furans and Their Application in Diels-Alder Reactions *Eu. J. Org. Chem*., **2001**, 2955-2964. (b) Watanabe, M.; Yoshie, N. Synthesis and properties of readily recyclable polymers from bisfuranic terminated poly (ethylene adipate) and multi-maleimide linkers *Polymer* **2006**, *47*, 4946–4952.

[12] Collins, L.A.; Franzblan, S.G.; Microplate alamar blue assay versus BACTEC 460 system for high- throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium *Antimicrob. Agents Chemother,* **1997***, 41*, 1004.

[13] Saito, H.; Tomioka, H.; Sato, K.; Emori, M.; Yamane, T.; Yamashita, K. In vitro antimycobacterial activities of newly synthesized benzoxazinorifamycins. *Antimicrob. Agents Chemother* **1991**, *35*, 542.

[14].(a) National Committee for Clinical Laboratory Standard. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeast, Approved Standard. Document M27-A; National Committee for Clinical Laboratory Standards: Wayne, PA, USA, 1997; (b) National Committee for Clinical Laboratory Standard. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium Forming Filamentous Fungi: Proposed Standard. Document M38-P; National Committee for Clinical Laboratory Standard: Wayne, PA, USA, 1998; (c) National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard, 5th ed.; NCCLS: Villanova, PA, 2000; pp M7–A5; (d) Yamamoto, N.; Fujita, J.; Shinzato, T.; Higa, F.; Tateyama, M.; Tohyama, M.; Nakasone, I.; Yamane, N. *Int. J. Antimicrob. Agents* **2006**, *27*, 171–173.