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

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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 the 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, antimicrobials*

Introduction

The Diels-Alder reaction is widely used to construct six-membered carbon skeletons in a wide variety of organic compounds of biological importance [1–3]. 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 [4–6]. Protein kinases are implicated in a number of biological processes and are the hot targets to explore new drugs and it is established that maleimides inhibit protein kinases [6]. 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 [7,8]. 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 [9–11]. The above reports and our quest for new antituberculars [12–15] 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

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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 ^1H 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 ($\mathcal{J}$) 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-diamino methyl-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–1 g)** (5.78 mmol) in toluene (7 mL), at 80°C and 1 equivalents of furfuryl amine (0.50 mL, 5.78 mmol) for 2–3 h 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 × 10 mL), saturated NaCl solution (2 × 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 maleimides **1f** and **1 g**.

*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 = 8.3 Hz, 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, $J_{2,6} = 8.3$ Hz, 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*, $\mathcal{J}_{8,9} = 2.8$ Hz and $\mathcal{J}_{8,7} = 1.6$ Hz, 1H, *H-8*), 6.26 (*d*, $\mathcal{J}_{8,9} = 3.0$ Hz, 1H, *H-9*), 4.02 (*m,* 3H, N*CH_2* and *H-7*), 3.03 (*d*, $\mathcal{J}_{2,6} = 5.9$ Hz, 1H, *H-6*), 2.99 (*d*, $\mathcal{J}_{6,2} = 5.8$ Hz, 1H, *H-2*), 2.73 (*d*, $\mathcal{J}_{2,6} = 5.1$ Hz, 1H, *H-6*), 2.64–2.62 (*d*, $\mathcal{J}_{6,2} = 5.1$ 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*, $\mathcal{J}_{8,9} = 3.0$ Hz and $\mathcal{J}_{8,7} = 1.7$ Hz, 1H, *H-8*), 6.28 (*d*, $\mathcal{J}_{8,9} = 2.9$ Hz, 1H, *H-9*), 4.13 (*m,* 3H, N*CH_2* and *H-7*), 3.18 (*d*, $\mathcal{J}_{2,6} = 8.3$ Hz, 1H, H-6), 3.11 (*d*, $\mathcal{J}_{6,2} = 8.3$ Hz, 1H, *H-2*), 2.82 (*d*, $\mathcal{J}_{2,6} = 5.6$ Hz, 1H, *H-6*), 2.73 (*d*, $\mathcal{J}_{6,2} = 5.6$ 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*, $\mathcal{J}_{8,9} = 1.9$ Hz and $\mathcal{J}_{8,7} = 1.8$ Hz, 1H, *H-8*), 6.27 (*d*, $\mathcal{J}_{8,7} = 2.9$ Hz, 1H, *H-9*), 3.99 (*m,* 3H, N*CH_2* and *H-7*), 3.10 (*d*, $\mathcal{J}_{2,6} = 8.3$ Hz, 1H, *H-6*), 3.01 (*d*, $\mathcal{J}_{6,2} = 8.3$ Hz, 1H, *H-2*), 2.70 (*d*, $\mathcal{J}_{2,6} = 5.2$ Hz, 1H, *H-6*), 2.61 (*d*, $\mathcal{J}_{6,2} = 5.9$ 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-dichlorophenyl)-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*CH2)*, 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-methoxyphenyl)-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 (1.11 mmol) and selected phenylisocyanates (1.14 mmol) in dry CH_2Cl_2 (2mL) was magnetically stirred at ambient temperature for 5–10 h 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 × 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* = 15.8 Hz, 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* = 4.3 Hz 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%].

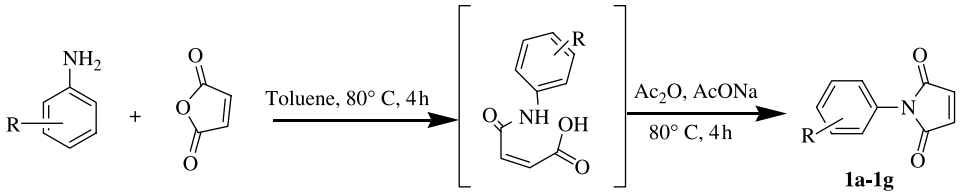
*1-(4-Chloro-phenyl)-3-(3,5-dioxo-4-(4-methoxyphenyl)-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-1-ylmethyl)-urea (**21**)*. white crystals (92.8%) yield, mp 170–173°C. *IR: (KBr) cm* $^{-1}$ 3420, 1718, 1597; *^{1}H-NMR (200 MHz, CDCl$_3$)*: δ 7.53 (*m*, 8H, *ArH*), 6.83 (*d,* J = 8.9 Hz, 1H, *H-9*), 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**–**1 g**) were prepared following earlier protocol [16,17] as shown in Scheme 1.



1a, R=H; **1b**, R= 4-CH_3;
1c, R=2-CH_3; **1d**, R=2,6-*di*- Cl;
1e, R= 4-OCH_3; **1f**, R=3-Br;
1g, R=3-OCH_3

Scheme 1. Preparation of N-phenyl maleimides.

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 1 g 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 [19]. 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, NCH2), 3.56–3.48 (*m*,1H, H-9), 2.71–2.63 (*m*, 2H, H-3ª 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 thermo-dynamically controlled exo-isomers predominates during reaction of maleimides with furfuryl alcohol [14].

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-chlorophe-nyl-, 2-flurophenyl-, 4-fluorophenyl-, 3-acetylphenyl-, 2-nitro-4-methoxyphenyl-isocyantes separately in CH_2Cl_2 under anhydrous condition.

All the compounds synthesized were evaluated against *Mycobacterium tuberculosis H37Ra* [21] and *Mycobacterium tuberculosis Rv* strains [22], *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 [23–26]. Antibacterial and antifungal screening results are shown in Table I.

The antimycobacterial activity of the above com-pounds 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

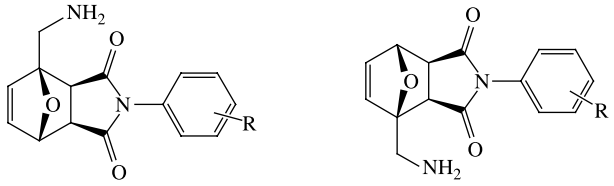
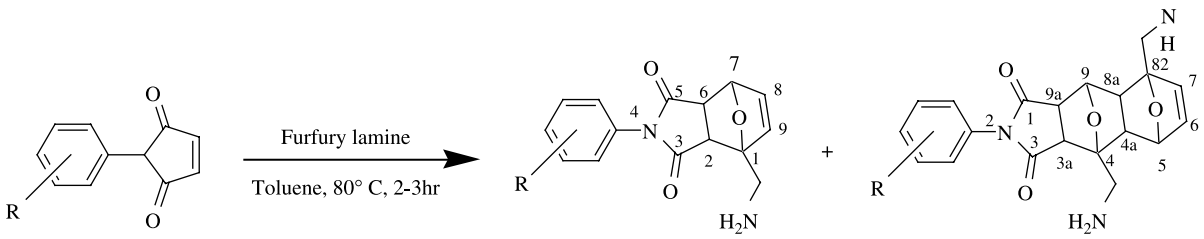


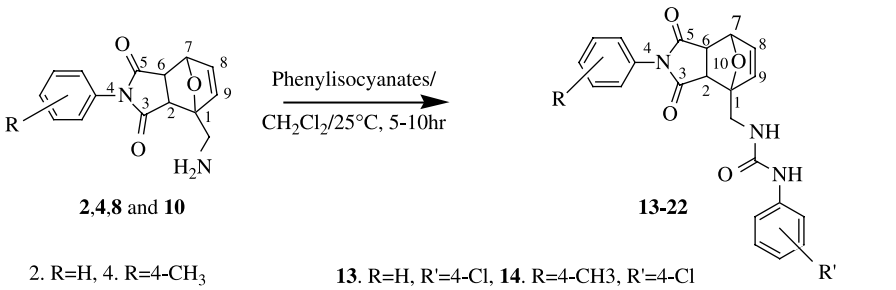
Figure 1. Structures of two exo-isomers.



1a-1g **2**,**4**,**6**,**8**,**10** **3**,**5**,**7**,**9**,**11**,**12**

2 and **3** R=H, **4** and **5** R=4-CH_3, **6** and **7** R=2-CH_3, **8** and **9** R=**2,4**-*di*-Cl, **10** R=**4**-OCH_3, **11** R=3-Br, **12** R=3-OCH_3

Scheme 2. Synthesis of azatricyclodiones and octahydro-benzo [f]-*iso*-in doles.



2. R=H, 4. R=4-CH_3
8. R=2, 6-*di*-Cl, 10. R=4-OCH_3

13. R=H, R'=4-Cl, **14**. R=4-CH3, R'=4-Cl
15. R=H, R'=4-OCH_3, 2-NO_2, **16.** R=4-CH_3, R'=4-OCH_3, 2-NO_2
17. R=2, 6-*di*-Cl, R'=4-OCH_3, 2-NO_2, **18**. R=H,R'=3-$COCH_3$
19. R=4-CH_3, R'=3-$COCH_3$, **20**. R=H, R'=2-F
21. R=4-OCH_3, R'=4-Cl, **22**. R=4-OCH_3, R'=4-F

Scheme 3. Synthesis of azatricyclicureides.

Table I. *In vitro* antibacterial antifungal activity

	Minimum inhibitory conc. (MIC) in μg/mL									
	BACTERIA				FUNGI					
Compound No.	1	2	3	4	5	6	7	8	9	10
2	>50	>50	>50	>50	>50	>50	50	25	>50	50
3	>50	>50	>50	>50	>50	>50	>50	50	>50	>50
4	>50	>50	>50	>50	>50	>50	50	25	>50	50
5	>50	>50	>50	>50	>50	>50	>50	50	>50	>50
6	>50	>50	>50	>50	>50	>50	50	50	>50	50
7	>50	>50	>50	>50	50	>50	50	50	>50	50
9	>50	50	>50	>50	>50	>50	50	50	>50	50
11	>50	>50	>50	>50	>50	>50	50	50	>50	50
12	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
13	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50

1. Klebsiella pneumoniae, 2. Escherichia coli 3. Pseudomonas aeruginosa, 4. Staphylococcus aureus, 5. Candida albicans, 6. Cryptococcus neoformans, 7. Sporothrix schenckii, 8. Trichophyton mentagrophytes, 9. Aspergillus fumigatus, 10. Candida parapsilosis (ATCC-22019)

no. **2** and **4** exhibited *in vitro* antifungal activity against *T. mentagrophytes* at 25μg/ mL (*Table I*).

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References

[1] Carruthers W. Cycloaddition reactions in organic synthesis. Oxford: Pergamon Press; 1990.
[2] Mulzer J, Altenbach HJ, Braum M, Krohn K, Reissig HU. Organic synthesis highlights. Weinheim: Verlag Chemie; 1991. p 54–70.
[3] Vogel P, Cossy J, Plumet J, Arjona O. Derivatives of 7-oxabicyclo[2.2.1]heptane in nature and as useful synthetic intermediates. Tetrahedron 1999;55:13521.
[4] Zhang HC, Derian CK, McComsey DF, White KB, Ye H, Hecker LR, Li J, Addo MF, Croll D, Eckardt AJ, Smith CE, Li Q, Cheung W-M, Conway BR, Emanuel S, Demarest KT, Gordon PA, Damiano BP, Maryanoff BE. Novel indolylindazolylmaleimides as inhibitors of protein kinase C-β: Synthesis, biological activity, and cardiovascular safety. J Med Chem 2005;48:1725–1728.
[5] Kalgutkar AS, Crews BC, Marnett LJ. Design, synthesis, and biochemical evaluation of N-substituted maleimides as inhibitors of prostaglandin endoperoxide synthases. J Med Chem 1996;39:1692–1703.
[6] Gayoso CW, Lima E, De O, de Souza EL, Filho VC, Trajano VN, Pereira F de Oliveira, Lima IO. Antimicrobial effectiveness of maleimides on fungal strains isolated from onychomycosis braz. Arch Biol Tech 2006;49:661–664.
[7] Kappe CO, Murphree SS, Padwa A. Synthetic applications of furan Diels-Alder chemistry. Tetrahedron 1997;53:14179.
[8] Tarducci C, Badyal JPS, Brewer SA, Willis C. Diels-Alder chemistry at furan ring functionalized solid surfaces. Chem Commun 2005;406–408.
[9] Cott D. J., Ziegler K. J., Owens V. P., Glennon J. D., Graham A. E., Holmes J. D.. Diels—Alder reactions between maleic anhydride and furan derivatives in supercritical CO_2 Green. Chem. 2005;7:05–10 and references.
[10] McCluskey A., Ackland S. P., Bowyer M. C., Baldwin M. L., Garner J. C., Walkom C., Sakoff J. A. Cantharidin analogues: synthesis and evaluation of growth inhibition in a panel of selected tumour cell lines. Bioorganic Chemistry 2003;31:68–79.
[11] Bailey TR, Rippin SR, Opsitnick E, Burns CJ, Pevear DC, Collett MS, Rhodes G, Tohan S, Huggins JW, Baker RO, Kern ER, Keith KA, Dai D, Yang G, Hruby D, Jordan R.

N-(3,3a,4,4a,5,5a,6,6a-Octahydro-1,3-dioxo-4,6- ethenocyclo-prop[f]isoindol-2-(1H)-yl)carboxamides: Identification of novel orthopoxvirus egress inhibitors. J Med Chem Letters 2007;50:1442–1444.

[12] Tripathi RP, Tewari N, Dwivedi N, Tiwari VK. Fighting tuberculosis-an old disease with new challenges. Med Res Rev 2005;25:93–131.

[13] Tripathi RP, Katiyar D, Tiwari VK, Tewari N, Verma SS, Sinha S, Gaikwad A, Srivastava A, Chaturvedi V, Srivastava BS, Tripathi RP. Synthesis and antitubercular activities of bis-glycosylated diamino alcohols. Eur J Med Chem 2005; 40:351–360.

[14] Tripathi RP, Tripathi R, Tiwari VK, Bala L, Sinha S, Srivastava A, Srivastava R, Srivastava BS. Synthesis of glycosylated beta-amino acids as new class of antitubercular agents. Eur J Med Chem 2002;37:773–781.

[15] Tewari N, Tiwari VK, Mishra RC, Tripathi RP, Srivastava AK, Ahmad R, Srivastava R, Srivastava BS. Synthesis and bioevaluation of glycosyl ureas as α-glucosidase inhibitors and their effect on mycobacterium. Bioorganic Med Chem 2003;11:2911–2922.

[16] Koechel DA, Tarloff JB, Rankin GO. Acute effects of alkylating agents on canine and renal function: Specifically designed synthetic maleimides. J Med Chem 1983;26:85–90.

[17] Tsou K-C, Barrnett RJ, Seligman AM. Preparation of some N-(1-naphthyl maleimides) as sulfhydryl group reagents. J Am Chem Soc 1955;77:4613–4616.

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

[19] Jarosz S, Mach M, Szewczyk K, Zbigniew SS. Synthesis of Sugar-Derived 2- and 3-substituted furans and their application in Diels-Alder reactions Eu. J Org Chem 2001; 2955–2964.

[20] 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.

[21] Collins LA, Franzblan SG. 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.

[22] 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.

[23] National Committee for Clinical Laboratory Standard. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeast. Approved Standard. Document M27-A Wayne, PA, USA: National Committee for Clinical Laboratory Standards; 1997.

[24] National Committee for Clinical Laboratory Standard. Document M38-P Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium Forming Filamentous Fungi: Proposed Standard. Wayne, PA, USA: National Committee for Clinical Laboratory Standard; 1998.

[25] National Committee for Clinical Laboratory Standards. Approved Standard Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 5th ed Villanova, PA: NCCLS; 2000. p M7-A5.

[26] Yamamoto N, Fujita J, Shinzato T, Higa F, Tateyama M, Tohyama M, Nakasone I, Yamane N Int J Antimicrob. Agents 2006;27:171–173.