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2,4-Bis(methylsulfanyl)pyrimidine *o*-quinodimethane: a versatile building block for functionalized fused pyrimidines

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ABSTRACT

Two alternative methods for the preparation of new pyrimidine Diels–Alder cycloadducts from the readily available 2,4-bis(methylsulfanyl)-5,6-dihydrocyclobuta[*d*]pyrimidine are presented. In the first method, the in situ generated pyrimidine *ortho*-quinodimethane reacts with various dienophiles to form the respective cycloadducts bearing two methylthio groups, which can be easily replaced by other functional groups. In the second method, one or both of the methylsulfanyl groups of the starting pyrimidine are replaced first and the resulting functionalized pyrimidines are able to undergo Diels–Alder cyclization with different dienophiles to form pyrimidine cycloadducts. These alternative synthetic strategies provide access to a wide variety of pyrimidine cycloadducts with a different substitution pattern on the pyrimidine ring. Yield data indicate that the electronic nature of the functional groups strongly influence the efficiency of the cycloaddition reaction.

1. Introduction

Fused pyrimidine derivatives are an important class of compounds with remarkable pharmaceutical applications. Thus, pyrrolopyrimidine derivatives inhibit the receptor tyrosine kinase enzymes.[1] Substituted thienopyrimidines are reported as insulin secretion enhancers[2] and for the treatment of inflammatory and immunoregulatory conditions.[3] Spiropyrimidines show a strong antibacterial and fungicidal activity.[4] On the other hand, *ortho*-quinodimethanes[5] (*o*-QDMs) (**1**), their heteroaromatic analogues[6] (**2**) and aza-*ortho*-quinodimethanes[7] (**3**) have been of interest as Diels–Alder dienes for the synthesis of various heterocyclic and organometallic compounds with potential pharmacological applications.[8] Homo and hetero Diels–Alder reactions of *o*-QDMs are employed as traceless linkers for solid-phase synthesis.[9] Normally, heteroaromatic *o*-QDMs (**2**) are generated in situ either thermally[10] or under microwave irradiation[11] from heterocyclic precursors that include sulfolene-fused heterocyclic compounds (**4**).[12] A variety of pyrimidine *o*-QDMs (**5**) formed either from sulfolene pyrimidinones[13] or from 2,4-disubstituted cyclobutapyrimidines[14] (**6**) can be trapped with different dienophiles (Chart 1). The use of 2,4-bis(methylsulfanyl)cyclobuta[*d*]pyrimidine[15] allows to exploit the different reactivity at positions 2 and 4 to carry out the independent chemical modification of each substituent. As a result, products having different substituents at these positions became readily available.[16]

In this paper we identify 2,4-bis(methylsulfanyl)-5,6-dihydrocyclobuta[*d*]pyrimidine (**7**) as a key versatile reagent for the generation of new 2,4-functionalized pyrimidine *o*-quinodimethanes. New functionalities (F^1 and F^2) can be introduced before or after the cycloaddition process to afford in an efficient way new Diels–Alder pyrimidine cycloadducts (Scheme 1).

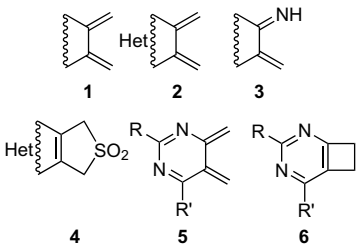

Chart 1. Homo-, hetero- and aza-quinodimethanes and precursors.

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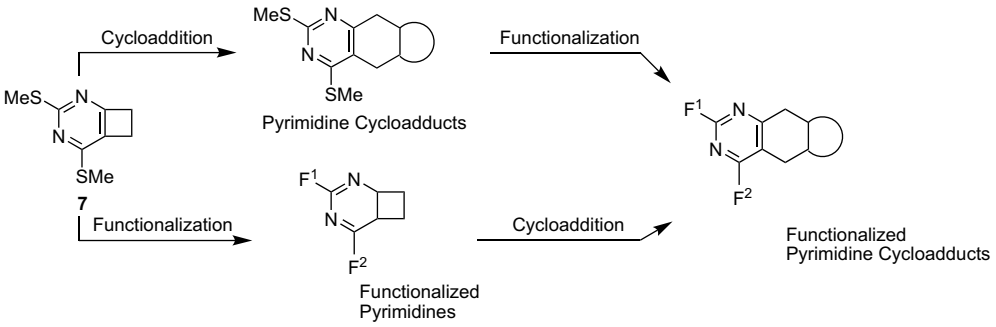


Scheme 1. Synthetic alternatives to functionalized pyrimidine cycloadducts.

2. Results and discussion

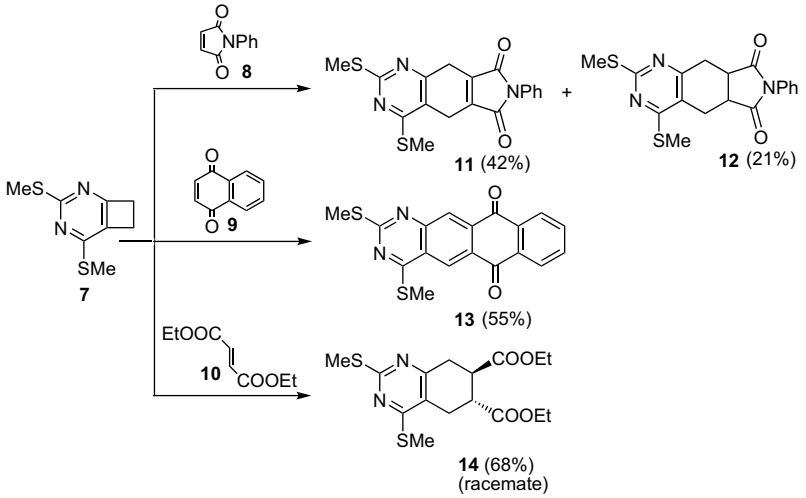
Following our general method,[15,17] 2,4-bis(methylsulfanyl)-5,6-dihydrocyclobuta[*d*]pyrimidine (**7**) was obtained in 40% yield in one step from a 1:2:1 molar ratio of cyclobutanone, methylthiocyanate and Tf_2O (triflic anhydride) in dichloromethane as solvent. In this reaction, the relatively low yield in which **7** is formed is due to the formation of side-products derived from the aldol condensation of cyclobutanone, as it has previously been observed either with aliphatic or aromatic nitriles.[18] Cycloadducts (**11**–**14**) were directly obtained by heating compound (**7**) with either *N*-phenylmaleimide (**8**), naphthoquinone (**9**) or diethyl fumarate (**10**) in *ortho*-dichlorobenzene (*o*-DCB) as solvent under reflux conditions (Scheme 2).

A strategic step in the synthesis of functionalized pyrimidines is the oxidation of both methylsulfanyl groups to methylsulfonyl to allow a further facile substitution by various nucleophiles.[16] Thus, oxidation of the pyrimidine adduct **12** with *m*-CPBA under mild conditions affords 2,4-bis(methylsulfonyl)pyrimidine adduct (**15**). Both methylsulfonyl groups are in turn easily substituted as it is exemplified by the reaction of **15** with sodium methoxide to give the expected dimethoxy product (**16**) in 50% yield (Scheme 3).

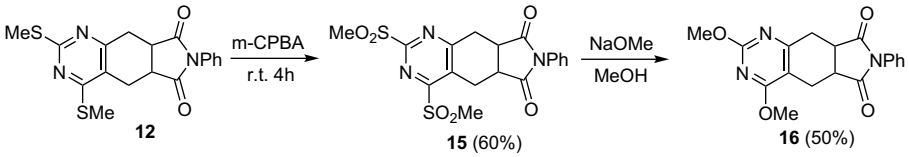
The alternative synthetic approach consists in an initial chemical modification of 2 and 4 positions at the pyrimidine ring, followed by the Diels–Alder reaction with formation of the respective adduct. Following a similar strategy, 2,4-bis(methylsulfanyl)-5,6-dihydrocyclobuta[*d*]pyrimidine (**7**) undergoes mild oxidation with *m*-CPBA (Scheme 4) thus transforming both methylsulfanyl groups to the corresponding methylsulfonyl groups. The methylsulfonyl groups can in turn be substituted by a different nucleophile.

2,4-Bis(methylsulfonyl)cyclobutapyrimidine (**17**) was found to be a highly versatile synthetic intermediate. As shown in Scheme 4, treatment with ammonia at atmospheric pressure yields 4-amino-2-methylsulfonyl-5,6-dihydrocyclobuta[*d*]pyrimidine (**18**) in a very good yield. Under harsher reaction conditions (120 °C), a double substitution takes place to give 2,4-diamino-5,6-dihydrocyclobuta[*d*]pyrimidine (**19**) in moderate yield. Treatment of **17** with sodium methoxide in methanol results in a double substitution of the methylsulfonyl groups to give 2,4-dimethoxy-5,6-dihydrocyclobuta[*d*]pyrimidine (**20**) in good yield.

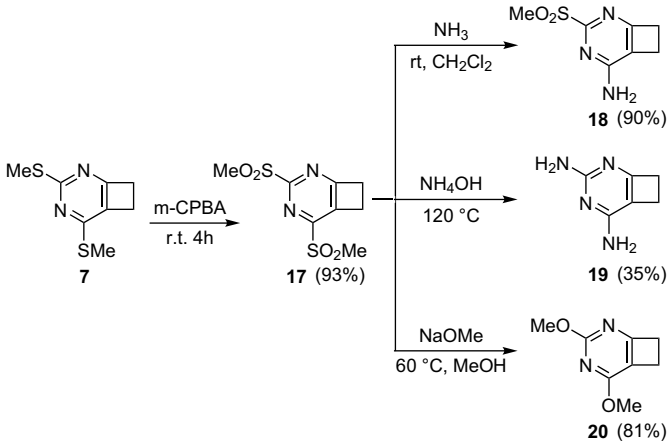
Following the replacement of the functional groups, cycloaddition with different dienophiles can be carried out (Scheme 5). Thus, thermal opening of the cyclobutane ring of disubstituted cyclobutapyrimidines (**21**) leads to the highly reactive pyrimidine *o*-quinodimethanes (**22**), further reaction of which with dienophiles (**8**–**10**) affords different doubly functionalized cycloadducts. Interestingly, the electronic nature of substituents F^1 and F^2 plays a decisive role in the yield and stereochemistry of the DA reaction. Theoretical calculations at the semiempirical level (PM3 and AM1) (Hyperchem v. 7.51) were used to predict the nature and geometry of cycloadducts. Table 1 indicates that energy differences HOMO(diene)–LUMO(dienophile) below 7.8 eV are sufficient to allow DA cyclization. Most of these adducts were formed in very good yields. However, 2,4-diamino-5,6-dihydrocyclobuta[*d*]pyrimidine (**19**) (having the most favourable energy difference) gave very poor yields. This can be explained by the thermal sensitivity of the amino groups to the harsh conditions (48 h, 180 °C). Bis(methylsulfonyl)pyrimidine **17** does not undergo Diels–Alder cyclization under the employed conditions due to the unfavourable HOMO orbital energy as well as on the thermolability induced by some



Scheme 2. Cycloadducts from **7** and *N*-phenylmaleimide (**8**), naphthoquinone (**9**) and diethyl fumarate (**10**).



Scheme 3. Oxidation of adduct **12** and subsequent reaction of **15** to form adduct **16**.

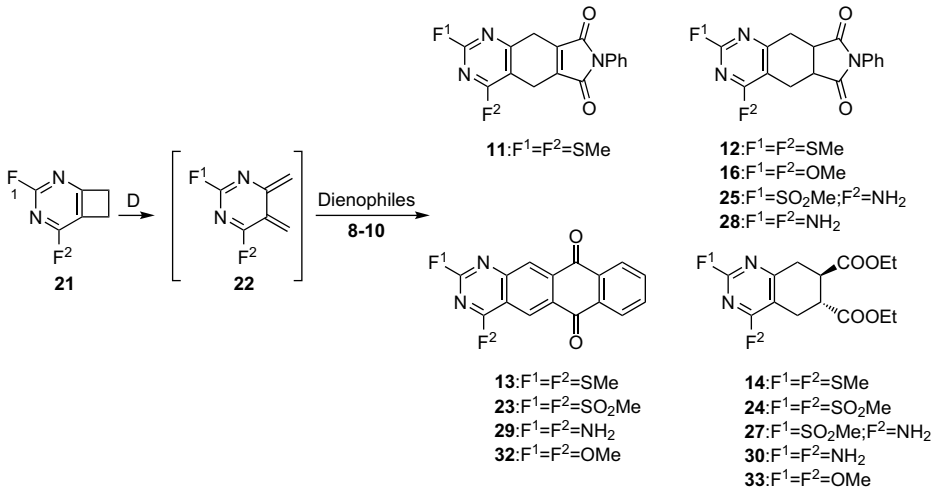


Scheme 4. Oxidation of (**7**) to 2,4-bis(methylsulfonyl)-5,6-dihydrocyclobuta[*d*]pyrimidine (**17**) and some functionalization possibilities.

confirm the proposed structure for the rearranged cycloadduct **31** (see Supplementary data).

Some cycloadducts were obtained only in very low yield, possibly due to the drastic reaction conditions needed to compensate the unfavourable ΔE(HOMO−LUMO) or to the thermal instability of the starting materials (Table 1). Nevertheless, the chemical versatility of the substituents F^1 and F^2 permits the straightforward and efficient preparation of these compounds by using simple reactions from readily available adducts. Thus, oxidation of **11** with *m*-CPBA leads to the formation of **34** in 87% yield. Compound **24** is obtained in 90% yield by oxidation of **14**, while uracil **35** is formed by acid hydrolysis of **32** in 90% yield (Scheme 7).

With regard to the stereochemistry observed for the Diels–Alder cycloadducts, homoaromatic *o*-QDMs are known to react with dienophiles by following the *endo*-addition,[19] pyridinone *o*-QDMs furnished cis-fused pyridinone cycloadducts corresponding to *endo*-addition,[20] and pyrazino *o*-QDMs cycloadd forming also the expected cis-adducts as a result of an *endo*-cycloaddition.[21] In our



Scheme 5. Cycloadducts formed from variously substituted cyclobutapyrimidines (**21**) and dienophiles (**8**–**10**).

substituents (see Supplementary data). In contrast, bis(methylsulfanyl) and dimethoxy pyrimidines (**7** and **20**) react easily with all the dienophiles forming the corresponding cycloadducts in very good yields. Although there are differences between the LUMO orbital energies of the dienophiles (**8**–**10**) (see Supplementary data), these differences do not seem to play any role in the obtained results. The choice of synthetic strategy (cycloaddition before functionalization or vice versa) will depend on this energy difference as well as on the thermolability of the substituents.

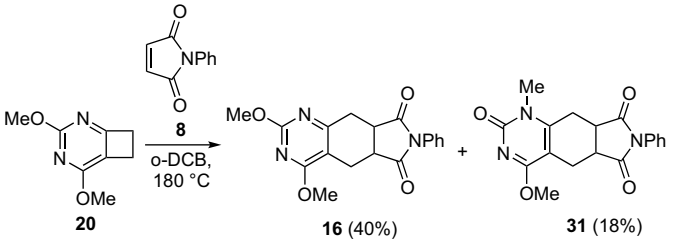
The reaction of pyrimidine **20** with dienophile **8** affords a mixture of the expected cycloadduct **16** together with a new and unexpected adduct **31** (Scheme 6). This compound results from the migration of the methyl group attached at the oxygen atom on position 2 to the N atom at position 1, presumably due to the harsh reaction conditions used. NMR experiments, including NOE, case, the stereochemistry of the cycloadducts obtained from *N*-phenylmaleimide (**8**) and the substituted dienes **36**–**38** derived from the corresponding cyclobutapyrimidines (Scheme 8) has been calculated using the semiempirical software described above. The results are summarized in Table 2 and indicate that the *endo* approach requires a lower energy path, as expected.

As a representative example, cycloadduct **16** exists as two conformers (**16A** and **16B**) with axial and equatorial orientation of the maleimide ring, respectively (Scheme 9). In order to distinguish between both conformers, NMR experiments were carried out on cycloadduct **16**. The proximity of the N atom of the pyrimidine ring causes the protons H9 to be less shielded than protons H5. Moreover, this proximity produces a decrease in the coupling constants for H9 protons. Irradiation of H5a and H8a at δ 3.54 ppm simplifies the spectrum allowing the total assignment and measurements of

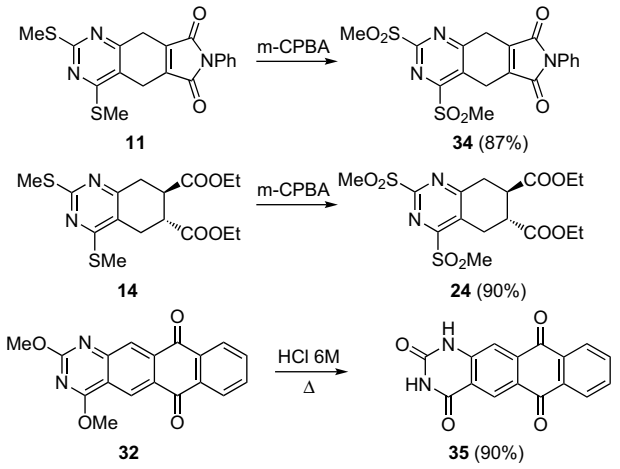
Table 1
Molecular orbital energies of dienes and dienophiles and yields of cycloadducts obtained in the direct Diels–Alder reaction (Scheme 5)

Adduct	Cyclobutapyrimidine	Dienophile	E_{Homo}[a] (eV)	E_{Lumo}[a] (eV)	$\Delta E_{Homo-Lumo}$ (eV)	Yield[b] (%)
F^1, F^2=SMe						
11+**12**	**7**	**8**	−8.237	−1.267	6.960	63
13	**7**	**9**	−8.237	−1.146	7.081	67
14	**7**	**10**	−8.237	−0.907	7.330	65
F^1, F^2=SO_2Me						
15	**17**	**8**	−9.735	−1.267	8.468	[c]
23	**17**	**9**	−9.735	−1.146	8.589	[c]
24	**17**	**10**	−9.735	−0.907	8.828	[c]
F^1=SO_2Me, F^2=NH_2						
25	**18**	**8**	−9.095	−1.267	7.828	45
26	**18**	**9**	−9.095	−1.146	7.949	[c]
27	**18**	**10**	−9.095	−0.907	8.188	[c]
F^1, F^2=NH_2						
28	**19**	**8**	−8.048	−1.267	6.781	[c]
29	**19**	**9**	−8.048	−1.146	6.902	[c]
30	**19**	**10**	−8.048	−0.907	7.131	[c]
F^1, F^2=OMe						
16	**20**	**8**	−8.661	−1.267	7.394	40+18[d]
32	**20**	**9**	−8.661	−1.146	7.515	66
33	**20**	**10**	−8.661	−0.907	7.754	59

[a] AM1.
[b] Percent yield of isolated product.
[c] Below 5%.
[d] Under the strong reaction conditions, 40% of adduct **16** and 18% of **31** were isolated (Scheme 6).

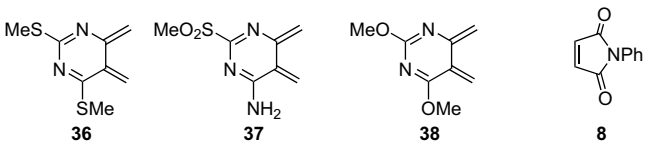


Scheme 6. Normal (**16**) and rearranged cycloadduct (**31**) obtained in the Diels–Alder reaction of **20** with *N*-phenylmaleimide (**8**).



Scheme 7. Synthetic alternatives to the preparation of cycloadducts **34**, **24** and **35**.

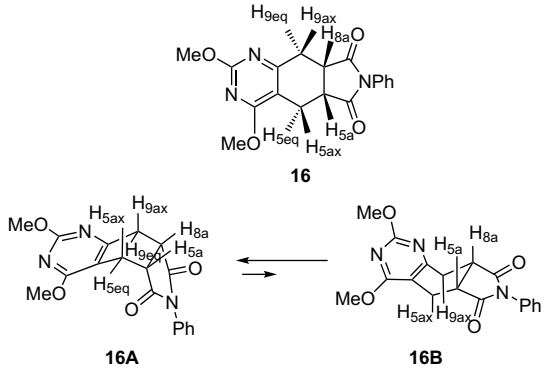
coupling constants. The measured values are in agreement with the expected values indicating a preferred axial orientation of the maleimide ring as in conformer **16A** (see Supplementary data).



Scheme 8. Dienes **36**–**38** and dienophile **8** used to predict the stereochemistry of adducts **12**, **25** and **16**.

Table 2
Calculated energy values (eV) for HOMO–LUMO interactions leading to the formation of cycloadducts

Pyrimidine *o*-QDM	Dienophile	Adduct	*endo*		*exo*	
			AM1	PM3	AM1	PM3
36	**8**	**12**	4.648	−13.762	13.636	−9.260
37	**8**	**25**	−61.444	−96.812	−60.633	−94.570
38	**8**	**16**	−49.725	−81.456	−48.739	−80.259



Scheme 9. Cycloadduct **16** and the two possible conformers for the *endo*-addition.

3. Conclusion

In summary, we report two new alternative and complementary synthetic paths to the preparation of new functionalized pyrimidine cycloadducts. This method allows the access to a large variety of pyrimidine-fused cycloadducts, which are otherwise unavailable. The electronic nature of the functional groups on the pyrimidine ring has a strong impact on the HOMO–LUMO energy levels and, therefore, on the course of the reaction and will determine the choice of the synthetic route to follow. As expected, experimental findings as well as theoretical calculations reveal that the stereochemistry of the obtained cycloadducts follows the *endo* rule.

4. Experimental

4.1. General

Dichloromethane was purified by distillation over P_2O_5. Triflic anhydride was prepared from TfOH[25] and distilled twice over P_2O_5 before use. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 at 300 and 500 MHz and 57 and 125 MHz and referenced to 7.26 and 77.00 ppm for chloroform and 2.50 and 39.5 ppm for DMSO, respectively. Due to the insolubility of compound **19**, the ^{13}C NMR spectrum was recorded in a mixture of DMSO-d_6 and methanol-d_4. Homonuclear *J* couplings were confirmed by single-frequency experiments. Multiplicity assignments of ^{13}C NMR signals were made from DEPT spectra. Homonuclear irradiation was used to simplify some complex nuclei systems and NOE spectra were used to confirm proposed structures.

4.2. 2,4-Bis(methylsulfanyl)-5,6-dihydrocyclobuta[*d*]pyrimidine (7)

Compound **7** was prepared from cyclobutanone, methythiocyanate and triflic anhydride following reported synthetic methods[15,18] in 40% yield, mp 102–103 °C (MeOH); IR (KBr) ν=1546, 1427, 1334 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.51 (s, 3H, SMe), 2.53 (s, 3H, SMe), 3.10 (t, J=3.9 Hz, 2H, CH_2), 3.30 (t, J=3.9 Hz, 2H, CH_2); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=11.5 (SMe), 14.2 (SMe), 27.1 (CH_2), 35.0 (CH_2), 129.5, 136.5, 161.6, 170.2 (arom); MS (EI) m/z 198 ($M^{+\bullet}$, 198), 183 (M−CH_3, 72), 137 (183−SCH_2, 19), 78 (21). Anal. Calcd for $C_8H_{10}N_2S_2$: C, 48.45; H, 5.08; N, 14.13; S, 32.34. Found: C, 48.31; H, 4.89; N, 13.98; S, 32.14.

4.3. General procedures for the functionalization of cyclobutapyrimidines

*4.3.1. 2,4-Bis(methylsulfonyl)-5,6-dihydrocyclobuta[d]pyrimidine (**17**)*

Compound **17** was prepared by oxidation from **7** according to the previously reported method[22] in 90% yield, mp 185–186 °C (EtOH); IR (KBr) ν=1620, 1427, 1176, 1072 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.21 (s, 3H, OMe), 3.27 (s, 3H, OMe), 3.56 (t, J=5 Hz, 2H, CH_2), 3.72 (t, J=5 Hz, 2H, CH_2); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=29.1 (CH_2), 38.3 (SO_2Me), 39.4 (CH_2), 39.6 (SO_2Me), 139.3, 156.2, 160.2, 181.3 (arom); MS (ESI) m/z 263 [M+H]$^+$. Anal. Calcd for $C_8H_{10}N_2O_4S_2$: C, 36.63; H, 3.84; N, 10.68; S, 24.45. Found: C, 36.50; H, 3.90; N, 10.53; S, 24.11.

*4.3.2. 4-Amino-2-(methylsulfonyl)-5,6-dihydrocyclobuta[d]pyrimidine (**18**)*

Compound **18** was prepared from **17** according to the previously reported methods[23] in 90% yield, mp 183–184 °C (EtOH); IR (KBr) ν=3495, 3300, 3120, 1404, 1190, 1010 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.95 (t, J=3.9 Hz, 2H, CH_2), 3.09 (s, 3H, SO_2Me), 3.19 (t, J=3.9 Hz, 2H, CH_2), 3.23 (s, 3H, SO_2Me), 3.87 (br s, 2H, NH_2); ^{13}C NMR (57 MHz, DMSO-d_6, 25 °C): δ=26.5 (CH_2), 34.0 (CH_2), 38.8 (SO_2Me), 121.0, 156.6, 157.4, 170.1; MS (EI) m/z (%B) 199 ($M^{+\bullet}$, 27), 184 (M−CH_3, 65), 120 (M−SO_2Me, 56), 42 (100). Anal. Calcd for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55; N, 21.09; S, 16.09. Found: C, 41.90; H, 4.33; N, 20.89; S, 15.87.

*4.3.3. 2,4-Diamino-5,6-dihydrocyclobuta[d]pyrimidine (**19**)*

A solution of **17** (0.20 g, 0.76 mmol) in ammonium hydroxide (20 mL) was heated at 100 °C in a pressure reactor (1.5 atm) for 24 h. The reaction mixture was extracted with dichloromethane (3×20 mL), washed with water (2×20 mL) and dried over sodium sulfate. The elimination of solvent affords a residue, which was purified by column chromatography (eluent EtOAc/hexanes=4:6). The target compound was obtained in 35% as undistillable oil; IR (film) ν=3500, 3400, 3300, 3200 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6+CD_3OD, 25 °C): δ=2.07, 2.21, 2.33, 2.39 (4H, AA′XX′system), 2.52 (s, 2H, NH_2), 3.19 (s, 2H, NH_2); ^{13}C NMR (57 MHz, DMSO-d_6+MeOD-d_4, 25 °C): δ=20.3 (CH_2), 33.5 (CH_2), 105.0, 129.7, 174.0, 184.4 (arom); MS (EI) m/z (%B) 136 ($M^{+\bullet}$, 37), 85 (33), 59 (47), 43 (100). Anal. Calcd for $C_6H_8N_4$: C, 52.93; H, 5.92; N, 41.15. Found: C, 52.70; H, 5.80; N, 40.92.

*4.3.4. 2,4-Dimethoxy-5,6-dihydrocyclobuta[d]pyrimidine (**20**)*

Compound **20** was prepared according to the previously reported methods[24] in 81% yield, mp 46–47 °C (MeOH); IR (KBr) ν=1211, 1085 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.03 (t, J=4 Hz, 2H, CH_2), 3.24 (t, J=4 Hz, 2H, CH_2), 3.93 (s, 6H, OMe); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=25.5 (CH_2), 34.6 (CH_2), 53.80 (OMe), 54.7 (OMe), 113.9, 163.5, 166.0, 175.2 (arom); MS (ESI) m/z 189 [M+Na]$^+$, 166 [M+H]$^+$. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.57; H, 5.88; N, 16.58.

4.4. Synthesis of cycloadducts. General procedure

A solution of the appropriate cyclobutapyrimidine (1 mmol) and the corresponding dienophile (**8**–**10**) (1.1 mmol) in *o*-dichlorobenzene (20 mL) was heated under reflux (180 °C) for a variable period of time. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the residue purified by column chromatography (eluent EtOAc/hexanes=5:95, 20:80 and 40:60). Further purification of the solid obtained was accomplished by recrystallization in the appropriate solvent.

*4.4.1. 2,4-Bis(methylsulfanyl)-7-phenyl-5H-pyrrolo[3,4-g]quinazoline-6,8(7H,9H)dione (**11**)*

Following the general procedure, the reaction of **7** with **8** affords the compound in 42% yield, reaction time 48 h, mp 208–209 °C (EtOH); IR (KBr) ν=1704, 1596, 1504, 1392 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.71 (s, 3H, SMe), 2.73 (s, 3H, SMe), 2.78 (t, J=7.4 Hz, 2H, CH_2), 3.49 (t, J=7.4 Hz, CH_2), 7.42 (m, 5H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=12.5 (CH_2), 14.1 (CH_2), 16.1 (SMe), 22.3 (SMe), 118.3, 123.2, 126.4, 128.0, 128.3, 129.1, 131.1, 157.3, 165.2, 166.2, 167.3 (arom); MS (EI) m/z (%B) 369 ($M^{+\bullet}$, 100), 354 (M−CH_3, 30), 336 (M−SH, 53), 329 (63), 77 ($C_6H_5^+$, 15), Anal. Calcd for $C_{18}H_{15}N_3O_2S_2$: C, 58.52; H, 4.09; N, 11.37; S, 17.36. Found: C, 58.37; H, 3.88; N, 11.11; S, 16.99.

*4.4.2. 2,4-Bis(methylsulfanyl)-7-phenyl-8a,9-dihydro-5H-pyrrolo[3,4-g]quinazoline-6,8(5aH,7H)-dione (**12**)*

Following the general procedure, the reaction of **7** with **8** affords the compound in 21% yield, reaction time 48 h, mp 189–190 °C (MeOH); IR (KBr) ν=1708, 1542, 1510, 1388 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.57 (s, 6H, SMe), 2.87–3.50 (two ABX systems, CH_2, CH), 7.14–7.40 (m, 5H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=12.7 (SMe), 14.2 (SMe), 23.5 (CH_2), 31.4 (CH_2), 39.0 (CH), 39.2 (CH), 119.5, 126.2, 128.7, 129.1, 131.5, 161.0, 177.1, 177.3 (arom); MS (EI) m/z (%B) 371 ($M^{+\bullet}$, 100), 356 (M−CH_3, 14), 338 (M−SH, 48), 223 (16), 191 (18), 77 ($C_6H_5^+$, 25). Anal. Calcd for $C_{18}H_{17}N_3O_2S_2$: C, 58.20; H, 4.61; N, 11.31; S, 17.26. Found: C, 58.05; H, 4.55; N, 11.11; S, 17.09.

*4.4.3. 2,4-Bis(methylsulfanyl)naphtho[2,3-g]quinazoline-6,11-dione (**13**)*

According to the general procedure, the reaction of **7** with **9** affords the compound in 55% yield, reaction time 48 h, mp 237–238 °C (MeOH); IR (KBr) ν=1674, 1591 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C)=ν 2.71 (s, 3H, SMe), 2.74 (s, 3H, SMe), 7.85 (m, 2H, Ar–H), 8.39 (m, 2H, Ar–H), 8.64 (s, 1H, Ar–H), 8.98 (s, 1H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=13.0 (SMe), 14.4 (SMe), 123.6, 125.8, 127.5, 127.7, 129.3, 134.0, 134.1, 137.0, 151.0, 170.8, 173.7 (arom), 181.6 (CO), 182.2 (CO); MS (EI) m/z (%B) 352 ($M^{+\bullet}$, 58), 337 (M−CH_3, 57), 83 (36), 72 (67), 59 (100). Anal. Calcd for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95; S, 18.20. Found: C, 61.19; H, 3.19; N, 7.57; S, 17.99.

*4.4.4. Diethyl(6R,6S,7R,7S)-2,4-bis(methylsulfanyl)-5,6,7,8-tetrahydroquinazoline-6,7-dicarboxylate (**14**)*

According to the general procedure, the reaction of **7** and **10** affords the compound in 68% yield, reaction time 48 h, mp 93–94 °C (hexanes); IR (KBr) ν=1733, 1527, 1313, 1184 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.23 (overlapped t, J=6 Hz, 6H, CH_2CH_3), 2.51 (s, 3H, SMe), 2.53 (s, 3H, SMe), 2.62 (m, 1H, CH), 2.87 (m, 2H, CH_2), 3.04 (m, 3H, CH, CH_2), 4.16 (overlapped q, J=6 Hz, 4H, CH_2CH_3); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=12.9 (CH_3CH_2), 14.1 (SMe), 25.7 (CH_2), 33.1 (CH_2), 40.7 (CH), 40.8 (CH), 118.8, 160.2, 168.2, 168.6 (arom), 169.9 (CO), 173.2 (CO); MS (EI) m/z (%B) 370

($M^{+\bullet}$, 51), 325 (M−OEt, 21), 297 (M−COOEt, 100), 223 (10). Anal. Calcd for $C_{16}H_{22}N_2O_4S_2$: C, 51.87; H, 5.99; N, 7.56; S, 17.31. Found: C, 51.61; H, 5.59; N, 7.40; S, 17.17.

4.5. General procedure for the functionalization of cycloadducts

The different procedures employed for the functionalization of cycloadducts are the same as reported above for the functionalization of cyclobutapyrimidines.

*4.5.1. 2,4-Bis(methylsulfonyl)-7-phenyl-8a,9-dihydro-5H-pyrrolo[3,4-g]quinazoline-6,8(5aH,7H)-dione (**15**)*

According to reported methods,[22] the oxidation of cycloadduct **12** affords **15** in 60% yield, mp 250 °C (decomp.) (EtOH); IR (KBr) ν=1716, 1398, 1315, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.52 (s, 3H, SO_2Me), 3.57 (s, 3H, SO_2Me), 3.67 (m, 6H, CH_2, CH), 7.24 (m, 2H, Ar–H), 7.46 (m, 3H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=12.7 (CH), 14.1 (CH), 23.5 (CH_2), 31.3 (CH_2), 38.9 (SO_2Me), 39.2 (SO_2Me), 119.5, 126.1, 128.6, 128.9, 131.4, 160.9, 167.5, 169.8 (arom), 177.1 (CO), 177.2 (CO); MS (EI) *m*/*z* (%B) 435 ($M^{+\bullet}$, 100), 403 (M−S, 11), 311 (97), 163 (44). Anal. Calcd for $C_{18}H_{17}N_3O_6S_2$: C, 49.65; H, 3.93; N, 9.65; S, 14.73. Found: C, 49.55; H, 3.69; N, 9.50; S, 14.44.

*4.5.2. 2,4-Dimethoxy-7-phenyl-8a,9-dihydro-5H-pyrrolo[3,4-g]quinazoline-6,8(5aH,7H)-dione (**16**)*

Following the general procedure, the reaction of **20** with **8** affords the compound in 40% yield, reaction time 48 h, mp 165–166 (EtOH); IR (KBr) ν=1705, 1541, 1375, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.85, 3.33 (ABX system, 3H, CH_2, CH), 3.11, 3.44 (ABX system, 3H, CH_2, CH), 4.01 (s, 6H, OMe), 7.15 (m, 2H, Ar–H), 7.37 (m, 1H, Ar–H), 7.43 (m, 2H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=20.6 (CH_2), 31.2 (CH_2), 39.3 (CH), 54.1 (OMe), 54.8 (OMe), 106.9, 126.9, 128.6, 129.0, 131.6, 169.9, 165.4, 168.0 (Ar–H), 177.6 (CO), 177.8 (CO); MS (EI) *m*/*z* (%B) 339 ($M^{+\bullet}$, 100), 324 (M−CH_3, 8), 309 (M−OMe, 10), 191 (97), 77 ($C_7H_7^+$, 18). Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.59; H, 4.91; N, 12.21.

*4.5.3. Diethyl (6R,6S,7R,7S)-2,4-bis(methylsulfonyl)-5,6,7,8-tetrahydroquinazoline-6,7-dicarboxylate (**24**)*

According to reported methods,[22] the oxidation of **14** leads to the formation of **24** in 90% yield, mp 139–140 °C (MeOH); IR (KBr) ν=1733, 1371, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.26 (overlapped t, *J*=6.5 Hz, 6H, C$H_3$$CH_2$), 3.29 (m, 2H, CH_2), 3.35 (s, 3H, SO_2Me), 3.45 (s, 3H, SO_2Me), 3.51 (m, 2H, CH_2), 3.58 (m, 1H, CH), 3.64 (m, 1H, CH), 4.19 (overlapped qt, *J*=6.5 Hz, 4H, CH_3CH_2); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=14.0 (C$H_3$$CH_2$), 14.1 (C$H_3$$CH_2$), 24.4 ($CH_2$), 33.0 ($CH_2$), 39.0 ($SO_2Me$), 39.3 ($SO_2Me$), 39.5 (CH), 39.7 (CH), 61.8 (CH_2CH_3), 128.5, 136.9, 162.2, 163.7 (arom), 172.0 (CO); MS (EI) *m*/*z* (%B) 434 ($M^{+\bullet}$, 22), 388 (M−EtOH, 87), 361 (M−COOEt, 100), 313 (81), 225 (44). Anal. Calcd for $C_{16}H_{22}N_2O_8S_2$: C, 44.23; H, 5.10; N, 6.45; S, 14.76. Found: C, 43.98; H, 4.90; N, 6.39; S, 14.60.

*4.5.4. 4-Amino-2-(methylsulfonyl)-7-phenyl-8a,9-dihydro-5H-pyrrolo[3,4-g]quinazoline-6,8(5aH,7H)-dione (**25**)*

According to the general procedure, the reaction of **18** with **8** affords the compound in 45% yield, reaction time 48 h, mp 272–273 °C (MeOH); IR (KBr) ν=3492, 1722, 1498, 1390, 1321 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=2.89–3.10 (m, 4H, CH_2, CH), 3.23 (s, 3H, SO_2Me), 3.55 (m, 2H, CH_2), 7.09 (m, 2H, Ar–H), 7.46 (m, 3H, Ar–H), 7.58 (br s, 2H, NH_2); ^{13}C NMR (57 MHz, DMSO-d_6, 25 °C): δ=26.5 (CH_2), 36.2 (CH_2), 44.0 (SO_2Me), 44.1 (CH), 44.2 (CH), 118.0, 132.0, 133.7, 134.1, 137.3, 166.5, 167.8, 168.2 (arom), 183.2 (CO), 183.3 (CO); MS (EI) *m*/*z* (%B) 372 ($M^{+\bullet}$, 34), 293 (21), 224 (40), 173 (100), 77 ($C_7H_7^+$, 72). Anal. Calcd for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04; S, 8.61. Found: C, 54.61; H, 4.23; N, 14.90; S, 8.59.

*4.5.5. 4-Methoxy-1-methyl-7-phenyl-5,5a,8a,9-tetrahydro-1H-pyrrolo[3,4-g]quinazoline-2,6,8(7H)-trione (**31**)*

Following the general procedure, the reaction of **20** with **8** affords the compound in 18% yield, reaction time 48 h, mp 115–116 °C (MeOH); IR (KBr) ν=1705, 1662, 1552, 1342 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.61 (AB system, *J*=10 Hz, 2H, CH_2), 2.83 (AB system, *J*=10 Hz, 2H, CH_2), 3.40 (m, 2H, CH), 3.59 (s, 3H, NMe), 3.98 (s, 3H, OMe), 7.13 (m, 2H, Ar–H), 7.40 (m, 1H, Ar–H), 7.46 (m, 2H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=20.9 (CH_2), 25.4 (CH_2), 32.0 (NMe), 38.4 (CH), 39.2 (CH), 54.4 (OMe), 100.7, 126.0, 128.8, 129.0, 131.1, 153.1, 156.6, 167.8 (arom), 177.0 (CO), 177.2 (CO); MS (EI) *m*/*z* (%B) 339 ($M^{+\bullet}$, 100), 309 (M−OMe, 25), 191 (97), 177 (20), 119 (36), 77 ($C_7H_7^+$, 18). Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.50; H, 4.96; N, 12.12.

*4.5.6. 2,4-Dimethoxynaphtho[2,3-g]quinazoline-6,11-dione (**32**)*

According to the general procedure, the reaction of **20** with **9** affords the compound in 66% yield, reaction time 48 h, mp 251–252 °C (MeOH); IR (KBr) ν=1682, 1589, 1508, 1394, 1309 cm^{-1}; ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=4.18 (s, 3H, OMe), 4.26 (s, 3H, OMe), 7.84 (m, 2H, Ar–H), 8.38 (m, 2H, Ar–H), 8.60 (s, 1H, Ar–H), 9.08 (s, 1H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=55.2 (OMe), 55.4 (OMe), 116.7, 126.0, 126.1, 127.6, 134.0, 134.1, 134.3, 134.5, 136.7, 158.3, 170.3, 175.1 (arom), 178.9 (CO); MS (EI) *m*/*z* (%B) 320 ($M^{+\bullet}$, 100), 305 (M−CH_3, 19), 290 (M−OMe, 43), 249 (23). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.33; H, 3.59; N, 8.61.

*4.5.7. Diethyl(6R,6S,7R,7S)-2,4-dimethoxy-5,6,7,8-tetrahydroquinazoline-6,7-dicarboxylate (**33**)*

According to the general procedure, the reaction of **20** with **10** affords the compound in 59% yield, reaction time 48 h, mp 175–177 °C (MeOH); IR (KBr) ν=1724, 1587, 1377, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.27 (overlapped t, *J*=7 Hz, 6H, CH_3CH_2), 2.60 (m, 2H, CH), 3.10 (m, 4H, CH_2), 3.93 (s, 3H, OMe), 3.97 (s, 3H, OMe), 4.20 (overlapped q, *J*=7 Hz, 4H, CH_2CH_3); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=23.7 (CH_3CH_2), 25.5 (CH_3CH_2), 33.2 (CH_2), 34.6 (CH_2), 41.0 (CH), 41.2 (CH), 54.0 (OMe), 54.7 (OMe), 61.0 (OCH_2), 61.7 (OCH_2), 107.4, 133.3, 134.7, 167.9 (arom), 173.5 (CO), 173.7 (CO); MS (EI) *m*/*z* (%B) 338 ($M^{+\bullet}$, 10), 293 (M−OCH_2CH_3, 15), 265 (M−COOEt, 100), 191 (55). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.55; H, 6.39; N, 8.09.

*4.5.8. 2,4-Bis(methylsulfonyl)-7-phenyl-5H-pyrrolo[3,4-g]quinazoline-6,8-(7H,9H)-dione (**34**)*

Following reported methods,[22] the oxidation of compound **11** affords cycloadduct **34** in 87% yield, mp 205–206 °C (MeOH); IR (KBr) ν=1718, 1388, 1307, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=3.03 (t, ^5J=7.2 Hz, 2H, CH_2), 3.52 (s, 3H, SO_2Me), 3.56 (s, 3H, SO_2Me), 4.09 (t, ^5J=7.2 Hz, 2H, CH_2), 7.45 (m, 5H, Ar–H); ^{13}C NMR (57 MHz, $CDCl_3$, 25 °C): δ=22.6 (SO_2Me), 25.4 (SO_2Me), 36.0 (CH_2), 40.8 (CH_2), 126.0, 126.4, 128.2, 129.1, 129.5, 129.8, 130.2, 131.1, 133.6, 134.2 (arom), 169.5 (CO); MS (EI) *m*/*z* (%B) 433 ($M^{+\bullet}$, 100), 354 (M−SO_2Me, 88), 273 (5), 77 ($C_6H_5^+$, 10). Anal. Calcd for $C_{18}H_{15}N_3O_6S_2$: C, 49.88; H, 3.49; N, 9.69; S, 14.80. Found: C, 49.65; H, 3.39; N, 9.48; S, 14.53.

*4.5.9. Naphtho[2,3-g]quinazoline-2,4,6,11(1H,3H)-tetrone (**35**)*

Cycloadduct **32** (0.20 g, 1.0 mmol) is suspended in aqueous HCl 6 M and heated for 6 h. The solvent was removed at reduced pressure and the residue washed with water and recrystallized. Uracil **35** was obtained in 90% yield, mp 260 °C (decomp.) (MeOH); IR (KBr) ν=3419, 3197, 1728, 1683, 1616 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 25 °C): δ=7.96 (m, 2H, Ar–H), 8.24 (m, 2H, Ar–H), 8.56 (s, 2H, Ar–H), 11.75 (br s, 1H, NH), 11.79 (br s, 1H, NH); ^{13}C NMR (57 MHz, DMSO-d_6, 25 °C): δ=114.4, 119.0, 127.7, 127.8, 128.0, 134.1,

134.2, 135.4, 135.8, 138.3, 145.7, 150.9 (arom), 162.8 (CONH), 181.6 (CO), 182.7 (CO); MS (EI) *m*/*z* (%B) 292 ($M^{+\bullet}$, 91), 249 (M−CONH, 100), 222 (23), 162 (19). Anal. Calcd for $C_{16}H_8N_2O_4$: C, 65.76; H, 2.76; N, 9.59. Found: C, 65.59; H, 2.67; N, 9.39.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.12.016.

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